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THOUGHTS ON THE STUDY OF ENDEMIC ICTEROHEMOGLOBINURIA BIOCHEMICAL MECHANISMS

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ABSTRACT:

`This article provides information on the discussion of the biochemical mechanisms of origin and development of endemic icterohemoglobinuria in karakul sheep grazing in the natural pastures of the Red Sand biogeochemical oasis on the basis of scientific sources and research results.

KEYWORDS: endemic icterohemoglobinuria, copper metabolism, hepatocytes, subcellular organelles, copper-containing proteins, radioactive copper, copper poisoning, pyrrolysidine alkaloids, metallotionine.

INTRODUCTION:

Specific experimental studies have shown that liver dysfunction and subsequent accumulation of large amounts of copper in sheep are caused by the consumption of alkaloids (heliotrin and its N-oxide) by the sheep - a hairy fruit heliotrope (Heliotropium dasycarpum) [[1,3].

This paper aims to analyze the scientific data on a particular problem and to substantiate the mechanisms of regulation of general homeostasis of copper in the body of karakul sheep based on the data of our special research on the distribution of copper in the subcellular elements of the liver cell, the activity of copper-containing enzymes in the blood and liver. The results of our study showed that in endemic ichtherohemoglobinuria, the amount of copper in the liver increases by 3 times or more. All subcellular fractions are involved in the accumulation of excess copper in the liver: the concentration of copper in large granules increases by 2.4 times, in the microsome fraction by 2.9 times, in the cytosol by 2.5 times, in the nucleus and cell fraction by 3.4 times.

A comparison of our data with data obtained by other authors shows that endemic icterohemoglobinuria is very similar to chronic copper toxicosis, which occurs experimentally in sheep and laboratory animals. In both cases, there was an increase in the amount of copper in the liver, with the proportion of the element in the nucleus and cell fraction fractions ranging from 59.4% to 78%, while the remaining fractions (coarse granules, microsomes and cytosol) together ranged from 22% to 40.6%. [2,10].

Given the specificity of copper metabolism in sheep, it is possible to make some considerations about the biochemical mechanisms of origin of endemic icterohemoglobinuria, which occurs in karakul sheep grazed on natural pastures of the Red Sands.

It is known that in the animal kingdom, there are two different types of copper metabolism that reflect the concentration of

copper in the liver. While the amount of copper in the liver of animals of the first type in adult animals is characterized by an amount of 100 mg / kg in dry mass, in the species of animals of the second type this figure is 30 mg / kg. While it is possible to include sheep in the first type of animal, rats can be included in the second type.

If the kinetics of radioactive copper in the body of sheep is described, it will be possible to construct a model of its exchange, in which the above three components should be considered as rings of a chain [13]. According to this model, copper is mainly directed to storage and to a lesser extent to the synthesis of bile and ceruloplasmin. Consequently, if the second increase in blood radioactivity due to the secretion of newly synthesized ceruloplasmin into the blood in rats occurs 14 hours after administration of 64Cu [7,8], in sheep this effect occurs 70 hours after injection [8]. Another difference is that while sheep have a correlation between the amount of copper in their diet and its concentration in the liver, rats do not have this type of correlation.

Based on the above evidence, it will be possible to consider these components in terms of the circulation of copper along certain components of the liver cell. Apparently, the first component is cytosol, in which copper binds to apoceruloplasmin in the form of a complex of amino acids and is partially secreted by bile in the form of a complex of amino acids and bile acids. The second component is the ribosomes and endoplasmic reticulum, where the synthesis of ceruloplasmin, superoxide dismutase, and some other copper-containing enzymes takes place.

In the mathematical modeling of radioactive copper metabolism, the main focus is on the synthesis of ceruloplasmin, as much of it is secreted into the blood and the remaining enzymes do not leave the hepatocyte. Therefore, the mathematical model cannot take into account the inclusion of copper in mitochondria and chromatin. The third component is the lysosomes that absorb metallothionein from the cytosol. The accumulation of the polymeric form of thionine in lysosomes has been proven by histochemical [11] and biochemical [4,6] methods. Studies have shown that metallotionein is a protein involved in the regulation of copper metabolism in the fetal and early postnatal stages of development, after which the synthesis of this protein is repressed in many animal species. In adult animals, the entry of heavy metals into the body [13], stress, as well as the synthesis of this protein under the influence of glucocorticoids (the most effective of which is dexamethasone) [4,13,14]. If the specificity of copper metabolism in sheep is replicated shortly after birth by the synthesis of metallothionein in other animal species, in them this process takes place only partially or not at all. Our observations of the presence of zinc-thionein in the liver under conditions of copper deficiency in our studies may serve as a basis for this hypothesis [2,3]. Due to its excess, the synthesis of these proteins is somewhat difficult due to the fact that metallotionine binds copper more strongly than other copper-bearing proteins. In all conditions in which the synthesis of metallotionine is increased, for example, in young children in Menkes and Wilson's disease, the synthesis of ceruloplasmin is not reduced in vain. The concentration of metallothionein in the blood of sheep is 2-4 times lower than in humans, rats and pigs, and its synthesis occurs 3 times slower in sheep than in rats. Thus, the copper content of copper in sheep is stronger than that of humans or rats. Metallotionein has also been shown to be present in several different iso forms.

In this regard, copper metabolism in sheep has a specific property, which can be explained by the fact that it is associated with the constitutional synthesis of metallotionine.

However, metallothionein is not the only copper-containing compound that is transferred to lysosomes. Lysosomes also include decomposition products of carbohydrate-neutral ceruloplasmin, superoxide dismutase (SOD), and other copper-proteins, but the proportion of metallothionein in quantities is high.

Thus, based on the above data, we will try to clarify the mechanisms of origin and development of ichtherohemoglobinuria in the body of karakul sheep grazed in the Red Sands pastures. It is known that in this biogeochemical oasis, when the pasture ration is at the level of normative indicators of copper metabolism, copper accumulates in the body and then reaches the level of copper poisoning. The onset of the disease begins with the presence of an alkaloid-containing plant in the sheep's diet, which alkaloids ensure strong absorption of copper by the liver and decrease its excretion through the bile, as well as its more stable binding with metallothionein. First, similar to the effects of heavy metals, it may enhance the synthesis of metallotionine due to derepression of the corresponding gene. This process occurs due to the alkylation of the corresponding repressor proteins. Increased metallotionein synthesis may also occur as a result of stress caused by toxicosis and under the influence of regenerative processes that enhance the synthesis of certain proteins [13]. Second, as a result of damage to plasma membranes by pyrrole metabolites [5], copper accumulated in hepatocytes may be inhibited by bile excretion from lysosomes [9,12]. A significant increase in the amount of copper itself can affect the secretory function of lysosomes, destroying the microtubules necessary for the movement of organelles by inhibiting the synthesis of tubulin protein [11]. In this case, the alkaloid pyrrolizidine disrupts copper exchange at the hepatocyte level, which in turn becomes a defective closed-chain system in the lysosomes, allowing the element to pass into the metalothontine and accumulate in the lysosomes, polymerizing it into an insoluble form. As a result, the synthetic, separation, and deposition processes associated with copper exchange between the subcellular components of the liver are radically disrupted. In particular, in farms unfavorable for endemic icterohemoglobinuria, it is promising to include in the diet of sheep an increased dose of zinc micronutrient, which has a depressant effect on the absorption of copper in the gastrointestinal tract and stabilizes the cytoplasmic membrane. Observations have shown that vitamin A has a similar effect. In the Red Sands, the cessation of exacerbation of icterohemoglobinuria in sheep on a green pasture diet in the spring is due to a similar effect. At the same time, our research has shown that this disease of sheep has a periodic character, there is a correlation between the quantitative indicators of moisture in pastures and the outbreak of the disease, as well as its cyclical nature [3]. Thus, it can be said that the disease does not occur when pasture food is diverse and can meet the daily needs of sheep without alkaloid-containing plants or by consuming them sparingly, when pasture food is poor, food needs begin to be met by alkaloid-containing plants and the disease progresses.

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