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Review

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Importance of selected bioactive substances of sheep milk for the development of young organisms

Znaczenie wybranych substancji bioaktywnych mleka owczego w rozwoju młodego organizmu

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Summary

Milk is the first food consumed by mammals. Its consumption is extremely important because of the nutritional value of milk and its ingredients which support the immune system of newborn babies. Some of the bioactive molecules pass into milk from the mother's blood and some are synthesized in the mammary gland. Sheep milk offers exceptional health benefits; it owes its properties to the rich chemical composition. This high health value of sheep's milk results from the presence of, inter alia, anti-oxidant substances such as CLA. Conjugated linoleic acid (CLA) is one of the most important anti-oxidants of milk fat, and exhibits anti--carcinogenic and anti-mutagenic effects. Hormones and their precursors are also present in milk, such as leptin. In sheep, the level of leptin is related to body fat content, food intake and the photoperiod length. The period of sexual activity of sheep depends on changes in the length of the day. Lactation is an essential part of the sheep's reproductive cycle. Correct functioning of the endocrine system is essential during lactation. And since proper rearing of offspring depends on the correct course of lactopoiesis, smooth interaction of all the processes is particularly important.

Keywords: **conjugated linoleic acid • orotic acid • leptin • milk**

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Abbreviations: **α-MSH** – α-Melanocyte-stimulating hormone; **AA** – arachidonic acid (omega-6); **ACTH** – adrenocorticotropic hormone; **AgPR** – Agouti protein; **ARC** – arcuate nucleus; **ATP** – adenosine triphosphate; **B9** – folic acid; **B12** – cobalamin; **CART** – cocaine and amphetamine-regulated transcript; **CLA** – conjugated linoleic acid; **DHA** – docosahexaenoic acid (omega-3); **EPA** – eicosapentaenoic acid (omega-3); **FSH** – Follicle-stimulating hormone; **GH** – growth hormone; **LDLs** – *low density lipoproteins*; **LEP** – leptin; **LH** – luteinizing hormone; **LHA** – the lateral hypothalamic area; **MC4R** – melanocortin type 4; **MCH** – the melanin concentrating hormone; **NPY** – neuropeptide Y; **OA** – orotic acid; **PUFAs** – polyunsaturated fatty acids; **POMC** – proopaemanocortin;

PRL – prolactin; **PRP** – proline-rich polypeptides; **PVN** – the ventricular nucleus; **SFAs** – saturated fatty acids; **SON** – the supraoptic nucleus; **TRH** – thyrolyberin; **TSH** – thyrotropic hormone; **VMH** – the ventromedial nucleus.

Lactation is an essential part of the sheep's reproductive cycle [11]. During pregnancy, it is possible to observe changes in the mammary glands, which prepare the ewes for lactation [9, 43]. The first food that newborn mammals receive is colostrum. Ingestion of colostrum by ruminant species (sheep, goats, cows) is a key factor in passing passive immunity and the overall survival of the newborn [21, 35]. Colostrum is rich in nutrients, such as polyunsaturated fatty acids (PUFAs), which include, inter-alia, omega-6 linoleic acid and omega-3 linolenic acid. In the human body, these acids are synthesized to produce their derivatives: omega-6 arachidonic acid (AA), omega-3 eicosapentaenoic acid (EPA) and omega-3 docosahexaenoic acid (DHA). These compounds perform such biological functions in the human organism as determining the structure of cell membranes; they are also a source of eicosanoids, or tissue hormones. Eicosanoids derived from omega-3 acids have anti-inflammatory, antithrombotic and anti-allergic properties [14]. Milk is the basic food for mammals in the neonatal period. Due to its chemical composition, it has unique health benefits, resulting, inter-alia, from the presence of antioxidant substances (conjugated linoleic acid - CLA, vitamins A and D, phospholipids, α-tocopherol, coenzyme Q10). These substances protect cells against damage caused by free radicals, so they are also anticancerogenic, and inhibit the oxidation of cholesterol, thus reducing the likelihood of atherosclerosis [17]. Studies have shown that CLA is the only fatty acid that inhibits tumorigenesis in animals [36]. In recent years, the theory that cancer incidence is linked to fat consumption has been gaining an ever-growing number of supporters. The so-called Greenland paradox is an argument against this very theory. Although fat accounts for more than half of the total energy value consumed in Inuit diet, the Inuit people do not suffer from atherosclerosis and neoplastic diseases [15]. Research shows that the underlying causes of diet-dependent metabolic disorders are disturbances in the pro- and anti-oxidant homeostasis of the body. It is known that tumor pathogenesis is associated with inflammation and accompanied by oxidative stress [6]. Fat consumption is one of the components of the diet determining the pro- and anti-oxidant homeostasis. Milk fat, due to its high content of saturated fatty acids (SFAs) and bioactive components with anti-oxidative activity, is beneficial for anti-oxidative homeostasis [16]. Conjugate linoleic acid (CLA), coenzyme Q10, vitamins A and E are the key anti-oxidants present in milk fat. Anti-oxidant properties are also demonstrated by phospholipids, vitamin D, ether lipids, cholesterol and 13-methyltetradecanic acid [27].

The most active milk fat anti-oxidant is conjugated linoleic acid (CLA) [5]. Ruminants synthesize CLA in two ways: one process occurs in the rumen, with the participation of *Butyrivibrio fibrisolvens* bacteria, and consists in the biohydrogenation of linoleic acid from the food; CLA is here an intermediate product of the conversion of unsaturated fatty acids into stearic acid. The second mechanism of CLA synthesis occurs in the mammary gland tissues, and takes the form of endogenous synthesis of the cis-9, trans-11 conjugated linoleic acid isomer from vaccenic acid in the rumen. Sheep milk is characterized by the highest content of the cis-9, trans-11 isomer among the ruminants [32]. The *trans* isomers present in milk fat have demonstrated health benefits. In countries such as Italy, France, where large quantities of cheeses rich in CLA are consumed, breast cancer mortality is lower compared to countries where cheese consumption is lower (Belgium, Netherlands) [8]. Milk fat is rich in immuno-stimulant and anti-oxidant ingredients, important in cancer prevention [41]. The cis-9, trans-11 isomer, has shown, both *in vitro* and *in vivo*, to inhibit the proliferation of tumor cells in, among others, the gastrointestinal tract, mamma, prostate, and the skin [50]. Research has confirmed the anti-carcinogenic and anti-mutagenic action of CLA. Conjugated linoleic acid, present in the diet, inhibited the development of chemically-induced gastric, dermal, breast and colon tumors in mice and rats. CLA might also have immuno--modulatory effects by influencing the function of lymphocytes and macrophages. Such effects have been demonstrated in studies on rabbits and hens, where the nature of CLA activity has been observed to consist in increasing cytotoxicity of T lymphocytes and phagocytic capacity of leukocytes and in neutralizing bacterial toxins [42]. A number of studies have proven the inhibitory effect of CLA on the development of tumor cells in, inter-alia, the mammary gland and prostate [12, 48]. Supplementation of CLA in a diet suppresses the proliferation of tumor cells and prevents metastasis. The anti-neoplastic function of linoleic acid dienes has been demonstrated; it has been shown that they reduce the incidence and decrease the development of chemically induced adenocarcinomas of the nipple in female rats [7]. In Finland, women who consumed full-fat dairy products had a lower incidence of cancer of the nipple. Conjugated linoleic acid acts cytostatically on intestinal and lung neoplasms and malignant melanoma [25]. It has been shown that a mouse diet enriched with *trans* 10, *cis* 12 C18:2 isomers allows for the reduction of fat tissue, improves lipid metabolism, increases muscle mass and inhibits the formation of atheromatous plaques [40]. Body weight decreases as a result of the following processes: increased energy expenditure, increased β-oxidation in skeletal muscles, decreased fat accumula-

tion in adipose tissue and/or differentiation of adipocytes by increased apoptosis and modulation of cytokines and adipokines, TNF-alpha, adiponectins or interleukins [40]. Fat accumulation is limited by way of inhibition of lipoprotein lipase, which is responsible for the transport of fatty acids and glycerol (necessary for the synthesis of adipose tissue) [4]. Health benefits of both milk and colostrum are used in the production of certain nutraceutics, which are used adjunctively to treat various diseases. A sheep colostrum product containing 11.3% natural CLA has a higher efficacy in inhibiting the growth of cancer cells compared to its counterpart with laboratory-synthesized CLA. Another mixture is colostrinin, a protein complex derived from sheep, cow or goat colostrum. Colostrinin - also known as proline-rich polypeptides (PRP) - shows immuno-modulating and psychotropic properties. It has a stabilizing and improving effect on the health of patients in the early or middle stages of Alzheimer's disease [26]. In addition, milk is a source of B group vitamins that participate in the synthesis and breakdown of carbohydrates, fats and amino acids, and are therefore essential in metabolic processes. Whey and sour milk is a particularly good source of orotic acid (vitamin B13). Orotic acid is a precursor of thymine, uracil and cytosine [49]; it lowers LDL cholesterol, has a lipotropic effect, reduces blood uric acid levels, contributes to the recovery of nucleic acids and the synthesis of proteins necessary for the body, and participates also in the metabolism of cobalamin (B12) and folic acid (B9) [26]. The presence of orotate in mammals is important to the development of the central nervous system [30]. Orotic acid, (OA; known under the names 2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid, 6-carboxyurine, animal galactose factor, whey factor, orotonin) plays a key role in the biosynthesis of pyrimidine bases. Complexes of orotic acid with metal exhibit anti-tumor activity [22]. Orotic acid is considered to be the precursor of all pyrimidine compounds present in living organisms [28]. Orotic acid demonstrates anti-carcinogenic properties, slows down the aging process, aids in the treatment of multiple sclerosis and improves liver function [39]. The importance of vitamin B13 in human metabolism also can be witnessed in individuals afflicted with orotic aciduria [47]. According to the literature available to the authors, nothing is known about the hypervitaminosis of this vitamin and about the adverse effects on the organisms.

Milk contains many substances whose specific levels are altered by various factors, as milk secretion is conditioned by a harmonious co-operation of many processes. During lactation, proper functioning of the endocrine system is required. Substances such as prolactin (PRL), thyrolyberin (TRH), thyrotropic hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone (GH), insulin, glucocorticoids, parathyroid hormone and calcitonin all play an important role. The correct course of lactopoiesis is a condition for the proper rearing of offspring [9]. In seasonal animals, day length is a factor modulating the secretion of metabolic hormones, especially leptin [3]. Hormones such as leptin, orexin and ghrelin are involved in maintaining the body's energy homeostasis. In the autumn-winter season, sheep are leptin-sensitive, but in the extended-day periods their sensitivity disappears [33]. In sheep, leptin levels are correlated with fat, food intake and the photoperiod [31]. It is possible that food intake and energy metabolism are modulated by orexin, via an interaction with leptin or melatonin [23]. Leptin (from Greek *lepto* - slim) is a protein with a molecular weight of 16 kDa, made up of 146 amino acids, and is a product of the Ob gene [50]. The locus of the leptin gene expression is the sheep's mammary gland [10]; it is secreted mainly by fat tissue and is present in the blood. Leptin levels are regulated by factors such as obesity, feeding intensity, energy balance, and the endocrine system [13]. Leptin is largely derived from differentiated adipocytes of the fat tissue, it is also secreted by the liver, placenta, small intestine epithelium, bone marrow cells, pituitary gland, skeletal muscles and the hypothalamus [20]. The plasma leptin concentration is directly proportional to the fat mass. LEP secretion is regulated by the circadian rhythm [29]. Leptin significantly affects the reproductive processes; Zang et al. observed that the ob gene mutation in mice resulted in infertility and obesity. Administration of leptin to mice inhibited the intake of food, decreased weight and restored fertility [48]. In adolescence, the increase in LEP levels contributes to the activation of the hypothalamic-pituitary-gonadal axis by stimulating the release of gonadotropin [18]. This confirms the hypothesis posited by Frisch and Revelle that it is necessary to reach a certain critical body mass for the consecutive stages of pubescence to occur [19]. LEP activates its receptors in the pituitary gland, increasing FSH and LH secretion, thus also affecting the hypothalamic-pituitary-gonadal axis [37]. Leptin not only controls reproduction, but also plays a role in controlling other processes, such as tissue metabolism, hormonal processes, blood pressure regulation, angiogenesis, steroidogenesis, hematopoiesis; it also modulates GH and PRL concentrations [34]. Leptin has many important functions in the body. The presence of leptin in milk suggests that this hormone could be involved in the physiology of the neonate [10]. As mentioned, leptin level is associated with food intake. Essential pathways of the hunger and satiety center are located in the arcuate nucleus (ARC). One type of neurons produces neuropeptide Y (NPY) and Agouti protein (AgRP) (melanocortin receptor antagonist), which are the main neurotransmitters responsible for the sensation of hunger. In the second type of neurons, neurotransmitters stimulating the sensation of satiety (melanotropic hormone α-MSH) and cocaine and amphetamine-regulated transcript (CART) peptides [45] are produced from proopaemanocortin (POMC). ARC neurons form anatomical-functional connections with other hypothalamic regions, such as the lateral hypothalamic area (LHA), the ventricular nucleus (PVN), and the ventromedial nucleus (VMH). Melanocortin type 4 (MC4R) receptors loca-

ted in the abdominal-medial nucleus are activated by POMC and CART, which results in experiencing satiety, while AgRP and NPY stimulate the release of orexins A and B and the melanin concentrating hormone (MCH) within the lateral hypothalamic area, and consequently intensify the sensation of hunger [44]. the Ob-Rb receptor expression was found in the ARC, VMH, LHA, PVN, and the supraoptic nucleus (SON). Stimulation of the Ob-Rb in the ARC by leptin and activation of intracellular JAK-STAT signal transduction cascade inhibit expression of the NPY and AgRP genes and the synthesis of these neurotransmitters. In addition, leptin and insulin cause the hyperpolarization of neurons synthesizing NPY and AgRP, by activating ATP-dependent potassium channels; also, as a result of this mechanism, they reduce their production [2]. In these processes, leptin inhibits the pathways responsible for the sensation of hunger (reduction of MCH and orexin production in the LHA). Leptin is an important negative regulator of food intake. Lack of active leptin receptors and impaired leptin secretion in animals promote the development of obesity and hyperphagia in animals [24]. In humans, abnormal leptin secretion or its excess causes the development of many immunological, metabolic and inflammatory disorders [38].

To summarize, milk is the first food consumed by mammals. Its consumption is extremely important because of the nutritional value of milk and its ingredients which support the immune system of newborn babies. Some of the bioactive molecules pass into milk from the mother's blood and some are synthesized in the mammary gland. Sheep milk offers exceptional health benefits: it owes its properties to the rich chemical composition. This high health value of sheep's milk results from the presence of, inter-alia, anti-oxidant substances such as CLA. Conjugated linoleic acid (CLA) is one of the most important anti-oxidants of milk fat, and exhibits anti-carcinogenic and anti-mutagenic effects. Hormones and their precursors are also present in milk, such as leptin. In sheep, the level of leptin is related to the body fat content, food intake and the photoperiod length. The locus of leptin gene expression is the sheep's mammary gland. Leptin is secreted mainly by fat tissue and is present in the blood, with its levels regulated by factors such as obesity, feeding intensity, energy balance, and the endocrine system. Correct functioning of the endocrine system is essential during lactation. And as proper rearing of offspring depends on the correct course of lactopoiesis, smooth interaction of all the processes is particularly important.

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