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The role of sheep colostrum bioactive substances in the organism's development

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Colostrum is the first secretion of mammals in the mammary gland. It is a unique food which provides offspring with all the necessary nutrients. Proteins and peptides play an important role in building immunity and developing the immune system. One of the main proteins is lactoferrin with anti-bacterial, anti-fungal, anti-viral and anti-cancer properties. The proline-rich polypeptide is also responsible for T cell maturation and inhibition of the development of autoimmune diseases. These proteins are easily absorbed, effectively support the development and protection of the body against pathogens. Colostrum bioactive substances are already used in the prevention and therapy of many diseases, especially those with a neurological basis. Due to the rich composition of bioactive substances and their health-promoting properties, sheep colostrum can be used in the prevention and treatment of autoimmune and neoplastic diseases, as well as many diseases of modern civilization.

Key words: sheep, colostrum, bioactive substances

Chemical composition of sheep colostrum

Colostrum is a thick yellow secretion containing a number of bioactive substances essential for the body. It is produced in the mammary glands of mammals already during pregnancy. Being the unique source of food for the neonate, colostrum provides all nutrients essential for development, considerable amounts of immunoglobulins, vitamins, mineral salts and growth factors (Barrington and Parish, 2001; Pierzynowski et al., 2014). With regard to chemical composition and biological properties, colostrum is considerably different in terms of parameters from milk proper, for which it is the precursor. Often termed as the elixir of life, it is most nutritious on the first day of lactation.

Chemical composition of colostrum is determined by genetic and environmental factors. Bovine colostrum contains around 13% of protein and around 7–8% of fat but these values change as lactation progresses (Kuczaj et al., 2006). Its chemical composition changes every hour from the onset of lactation until colostrum changes to milk proper (Field, 2005). Greatest fluctuations in ovine colostrum components occur during the first 72 hours after parturition (França et al., 2010). Over the first 6 hours, protein content decreases considerably from 21.7 to 13.95% (Ciuryk et al., 2004). In the case of non-essential amino acids, the strongest decline is observed within 12 hours of parturition. Aspartic acid decreased by more than 40%, from the initial 1454 mg/100 ml to 654 mg/100 ml. Similar relationships were found for the other amino acids: serine, glutamic acid, proline, glycine, alanine and tyrosine, the concentrations of which fell by as much as 64%. The arginine and valine content during the first 12 hours after parturition decreased by 25%, histidine by 30%, methionine, lysine and isoleucine by 35%, leucine and threonine by 40%, cysteine and phenylalanine by 50% (Kráčmar et al., 2005). The rate of change in colostrum amino acid content during the first hours after parturition is associated in particular with a rapid decline in the amount of serum proteins, especially immunoglobulins, and with a decreasing level of free peptides and amino acids. Over the next hours, the amount of amino acids and their proportions in colostrum are significantly influenced by increasing proportion of the casein fraction, which is associated with colostrum changing into milk proper (Kráčmar et al., 2005).

In sheep, significant changes in fat content are also taking place during the first 72 hours after lambing. The content of fat increases to 14.1% over the first 6 hours, but decreases to 10.05% at 12 hours and to 6.55% at 72 hours after lambing (Ciuryk et al., 2004). The changes in fat content modify the profile of fatty acids, which are a significant factor in the nutritional properties of colostrum. During the first 12 hours after parturition, the concentration of saturated fatty acids (caproic, caprylic, capric) in colostrum shows no significant changes. The content of all saturated fatty acids increases with advancing lactation by around 3%. The content of short-chain fatty acids in colostrum is lower than in milk. The concentration of margaroleic acid decreases and that of oleic acid increases with time after lambing. The content of unsaturated fatty acids slightly declines with progressing lactation, from 38.5 to 37.15% after 72 hours (Ciuryk et al., 2004).

In mammalian colostrum, not only protein, fat, solids and fatty acids undergo dynamic changes. There are also significant alterations in the content of micro- and macroelements, which has an effect on the development of a young organism. Calcium (Ca) content decreases sharply between two and twelve hours after parturition. Later on Ca content increases from 10.1 to 19.5%. Similar changes are observed for the concentration of phosphorus (P), which increases significantly from 4.8 to 13.5%. Magnesium (Mg) content shows a downward trend over 12 hours, decreasing from 13.08 to 8.67 mmol/1000 ml. During the first 36 hours after parturition, sodium (Na) concentration falls from 28.48 to 17.68 mmol/1000 ml to slightly increase to 18.70 mmol/1000 ml. A reserve trend is observed for potassium (K), the concentration of which increases over the first 36 hours (from 40.37 to 45.85 mmol/1000 ml), and decreases to 38.87 mmol/1000 ml. The concentration of trace elements also declines with advancing lactation. The level of zinc (Zn) decreases within the first 36 hours from 3.40 to 0.94 mol/1000 ml, and a similar trend occurs for the content of iron (Fe). The concentration of copper (Cu) decreases during the first 48 hours after birth, from 0.22 to 0.16 mol/1000 ml, and later to 0.10 mol/1000 ml (Kráčmar et al., 2005).

Role of colostrum in the development of young organism

Colostrum is the unique source of food, providing the neonate with essential nutrients. In the case of sheep, a lamb requires around 180–290 ml of colostrum/kg of body weight during 18 hours after birth. The energy value of colostrum is around 2 kcal/ml. Within the first hours after birth, lambs must increase 15-fold their energy expenditure on heat production in relation to the prenatal period so as to maintain adequate body temperature. To keep body temperature, neonates, prior to first ingestion of colostrum, metabolize the accumulated stores of brown fat and increase activity of their muscles, causing them to tremble. Brown fat is the principal source of energy, but it constitutes only 2–4.5% of the lamb's body weight. Because the stores of fat are disproportionately low in relation to energy expenditure early in life, it is essential that the lamb is provided with colostrum of adequate quality (Hadjipanayiotou, 1995). Colostrum is the first food for newborn mammals, rich in proteins and peptides that play an important role in enhancing the immunity of a young organism and in developing the immune system. Around 25% of the immunoglobulins ingested with colostrum enters the lamb's circulation. Because passive absorption in the intestine terminates 24 hours after birth, any delay in feeding colostrum or its low quality reduce the lamb's chances of acquiring adequate immunity (Nowakowski et al., 1992). Storage of immunoglobulins takes place due to receptors present in the mammary epithelial cells and subsides several days after the onset of lactation in response to increased prolactin concentration in milk (Misztal et al., 2018). In addition to immunoglobulins, mother's colostrum also carries active immune cells and soluble mediators such as lactoferrins. Animals that have not received lactoferrin early after birth are characterized by lower immunity and dysfunction of neutrophils, whch are the main barrier against pathogenic microorganisms. The neonate's small intestine enterocytes have the unique capacity for absorbing protein macromolecules, including immunoglobulins, via pinocytosis. Proteins are protected from digestion in the digestive tract through low protease activity immediately after birth and by the presence of trypsin inhibitor in the colostrum. Thereafter, antibodies are transported to the lymphatic system via exocytosis. The lower absorption capacity is associated with the exhausted capacity of intestinal cells for pinocytosis as well as with the replacement of enterocytes by adult intestinal epithelial cells (Lonnerdal and Iyer, 1995).

Of special significance are proteins, which provide offspring with all essential amino acids while protecting against pathogens and stimulating the development of immunity. The most important protein affecting the development of a young organism is lactoferrin (LF), which exhibits a number of antimicrobial and immunotropic properties. It shows activity against many bacteria, viruses, fungi and many types of parasites. Lactoferrin accounts for around 30% of all proteins in colostrum and has a concentration of around 5–15 mg/ml, which provides the neonate with high amounts of this protein during nursing (Lonnerdal and Iyer, 1995). LF has a very low susceptibility to digestive enzymes in the small intestine, such as trypsin and chymotrypsin. It is important that protein should survive the digestive process, such that the active protein form remains in the intestine long enough, but even when partially degraded, it maintains many of its functions. Similar activity to that of lactoferrin is shown by protein hydrolyzates, especially those containing a lactoferricin fragment rich in basic amino acids and in other lactoferrin-derived peptides (Brines and Brock, 1983). Young organisms have a poorly developed intestinal barrier and show low enzymatic activity, which allows for absorbing high amounts of protein from the digestive tract into the blood and its subsequent presence in the serum, urine and cerebrospinal fluid. Lactoferrin stimulates intestinal immunity and affects the systemic immune response by stimulating cytokine production, myelopoiesis induction, and proliferation and growth of immune cell activity (Debbabi et al., 1998). LF facilitates the absorption of essential nutrients, mainly elements such as iron and manganese, and also facilitates the absorption of carbohydrates in the intestine (Ogata et al., 1998). Lactoferrin enhances the growth of small intestine length and weight, and has protective effects on intestinal epithelium. This is crucial due to the contribution of the intestine to active absorption of food and its functions related to protecting the body against harmful pathogens and antigens found in food. The effect of lactoferrin on maturation of intestinal mucosa reduces infections related to the passage of bacteria from the intestine to the blood (Schottstedt et al., 2005). Furthermore, LF limits the growth of pathogenic microflora, which hampers the adhesion of harmful bacteria to intestinal epithelial cells, and stimulates the growth of natural flora of lactic acid bacteria (*Lactobacillus*) and *Bifidobacterium*, which further protects against microbial infections and microbial overgrowth. The colostrum-derived symbiotic bacteria of gut microflora are responsible for several beneficial processes such as production of organic acids that reduce intestinal pH, stimulation of colonic epithelium growth, reduction of serum cholesterol concentration, inhibition of cancerous agents, and production of K and B vitamins. These bacteria control pathogenic microflora by competing for nutrients, saturate receptors on the surface of epithelial cells, stimulate production of natural antibodies, and increase the activity of natural killer cells, T lymphocytes and macrophages (Weinberg, 2001). The administration of protein, in doses as high as 2–7 mg per day, is well tolerated and elicits no adverse effects. Due to a host of properties influencing the development of a young organism, it seems appropriate to supplement colostrum and other products containing isolated lactoferrin (Artym and Zimecki, 2005).

Application of colostral bioactive substances in medicine and pharmacy

Owing to the rich composition of bioactive substances and their health-promoting properties, a number of studies were performed which showed the usefulness of colostrum in the prevention and treatment of autoimmune and neoplastic diseases, stimulating the recovery of the immune system after chemotherapy, and counteracting infections, sepsis and bacteremia. Specific properties are shown by colostral proteins and peptides, such as lactoferrin, proline-rich polypeptides (PRP), casein, glycomacropeptide (GMP), lactalbumin (LA), lactoglobulin, lysozyme (LY) and lactoperoxidase (LCP) (Artym and Zimecki, 2005).

Lactoferrin (LF) belongs to a family of proteins involved in iron metabolism, and its concentration in colostrum is ten times that in milk. Being the basic component of innate immunity system, it shows a wide variety of protective and immunotropic properties. LF shows antibacterial and bacteriostatic activity by stimulating immunity and, directly, by damaging the cell walls and altering the metabolism of bacteria. It binds to porin proteins of the Gram-negative bacterial cell wall, which disrupts nutrient permeability and compromises its structure. It is also able to release from the bacterial wall the lipopolysaccharide (LPS) that protects porins from interacting with LF, which causes bacteria to die (Sallman et al., 1999). Direct antibacterial effect was also established for enzymatic hydrolyzates of lactoferrin, such as lactoferricin, which binds to *Escherichia coli* and *Bacillus subtilis* to inhibit proline absorption, leading to their degradation. Another peptide that shows activity against *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* is lactoferrampin. It also exhibits antifungal activity against parasitic fungi such as *Candida* (Bellamy et al., 1993). Lactoferrin interacts with lysozyme protein in the process of bacterial wall destruction, further stimulating the immune system through its presence in intestinal epithelium secretions and granular neutrophils. Lactoferrin prevents the synthesis of IgA protease of *Escherichia coli* bacteria wall and destroys Hap adhesin, thus preventing adhesion of the bacteria to enterocytes and HeLa cells while accelerating the removal of bacteria from blood (De Araujo and Giugliano, 2001). Another important antibacterial property of lactoferrin is its capacity to bind iron, which limits its availability to bacteria, and also protects the organism against production of toxic forms of oxygen and free radicals, thus reducing the generation of inflammatory processes (Weinberg, 1986). Lactoferrin administration increases neutrophil production and limits production of tumor necrosis factor (TNF-α), ameliorates the course of infections in organisms with a lower number of granulocytes caused by chemotherapy. In fighting against bacterial infections, lactoferrin has the capacity to reduce resistance of bacteria to antibiotics such as vancomycin, penicillin and cefpodoxime (Diarra et al., 2002). In inflammatory processes, this protein stimulates the production of anti-inflammatory cytokines and seals epithelium, thus influencing intestinal blood barrier efficiency, which prevents pathogens reaching the blood from the digestive system. Lactoferrin prevents the development of endotoxemia by preventing the binding of endotoxin to cell surfaces and reacts with the receptors responsible for the pathogen, thus protecting the organism from overreaction of the immune system through endotoxin and from development of shock (Appelmelk et al., 1994). In fungal infections it is toxic to pathogens, and through iron chelation it reduces access to this element and efficiently inhibits the development of mycosis. It also accelerates the body's regeneration after infection. Preparations containing exogenous human lactoferrin increase the efficiency of conventional fungal infection treatment methods by reducing the requirement for drug doses, and are also effective in therapy against drug-resistant fungi by increasing their sensitivity to the preparation through the effect of protein on mitochondrial respiration processes. Lactoferrin also found application in antiparasitic therapy as it inhibits the development and multiplication of protozoa. This is because the protein binds iron, leading to the generation of free radical complexes that damage the cell membranes of infected cells and of parasites. Furthermore, it stimulates phagocytosis and killing of parasites through blood monocytes (Lupetti et al., 2003). This protein is also beneficial in the prevention and treatment of viral infections. It is effective against viruses such as the herpesvirus, HIV, hepatitis B and C, hantaviruses, rotaviruses, polioviruses, adenoviruses and enteroviruses, mainly by preventing the absorption and entry of pathogens into cells by interacting with viruses and stimulating the body's immune system (Van der Strate et al., 2001). In treating hepatitis C viral infections, it specifically binds virus envelope protein E2, preventing entry of the virus into the cell. In fighting HIV, it blocks CXCR4 and CCR5 chemokine co-receptors, binds to surface proteins of the virus (gp120), and also binds to lectin-type receptors, which prevents the virus from fusing with the cell. Lactoferrin also reduces the proliferation of the virus by inhibiting the activity of reverse transcriptase, protease and integrase as well as HIV-1 enzymes, essential to the replication process. In papilloma, herpes simplex, adenovirus and cytomegalovirus (CMV) infections, lactoferrin acts by competing with pathogens for attaching to the glycosaminoglycan receptor, preventing it from fusing with the cell (Drobni et al., 2004). Like in bacterial, fungal and parasitic infections, it supports the action of antiviral drugs by increasing their effectiveness, which allows reducing the drug doses (Van der Strate et al., 2001). Lactoferrin and its derivatives also find many applications in the treatment of cancers. They show cytotoxic action by damaging cancer cell membranes, leading to necrosis and reduction of tumour size, inhibit angiogenesis within tumours, and affect iron sequestration by preventing the generation of vessels responsible for delivery of oxygen and nutrients to cancer cells, which counteracts the development of tumours and metastases (Eliassen et al., 2002). This protein also shows analgesic action and increases the effectiveness of morphine by activating the body's endogenous opioid system. Lactoferrin has a great influence on development, stimulation and regeneration of the immune system. LF interacts with thymus cells which are precursors of T helper cells, which increases the humoral response of the immune system, promotes maturation of B lymphocytes in the spleen, which is associated with an increased number of surface IgD, and also increases the capacity of these lymphocytes for presenting antigens to T helper cells. LF increases the activity of leukocytes and lymphocytes and prevents a decrease in their number. It also has a favourable effect on reducing histological changes in the liver and stimulating cytokine production (Eliassen et al., 2002).

In addition to lactoferrin, proline-rich peptides (PRP), identified in ovine colostrum, find extensive medicinal use. These peptides stimulate the humoral immune response, increase permeability of blood vessels, stimulate delayed type hypersensitivity reactions and support thymocyte maturation. PRP have a beneficial effect on T cell precursor stimulation, cytokine induction, and decrease the level of antibodies produced. Furthermore, they enhance cognitive function and daily activity in Alzheimer patients, among others by reducing production of nitric oxide in the body (Staroscik et al., 1983).

A number of health-promoting properties is shown by casein found in colostrum and also by its peptides. One property of this protein is that it protects tooth enamel from degradation by binding to dental plaque, which also inhibit the development of caries. Casein phosphopeptides have an effect on calcium and phosphorus metabolism by regulating bone mineral density and preventing bone losses. This protein also shows protective action in bacterial infections and sepsis, stimulates systemic response to infections and production of IgA, which play an important role in protecting intestinal tissue from the entry of pathogens. Sheep casein hydrolysates also find application in prevention and treatment of diabetes through neogenesis of the islets of Langerhans, responsible for regulating metabolic processes associated with sugar balance in the body. This protein is also used to treat neoplastic diseases as it reduces the number of tumours and their mass. In addition, it stimulates the production of glutathione, an anticancer and antioxidant peptide in the liver. Casein hydrolysates are effective in reducing blood pressure by inhibiting the activity of the enzyme that converts angiotensin I to the active form angiotensin II, which contributes to vasoconstriction. Peptides isolated from casein are analgesic and show tranquilizing properties similar to opioids (Otani et al., 2003).

A casein hydrolysate with a high content of sialic acid is glycomacropeptide (GMP), which contributes to macrophage development by stimulating phagocytosis. Furthermore, GMP prevents adhesion of bacteria colonizing the oral cavity to erythrocytes, shows anti-aggregation and antithrombotic properties, and increases food absorption. This peptide also finds application in the treatment of blood infections and sepsis (Brody, 2000).

Lactalbumin and lactoglobulin fight HIV by inhibiting viral enzymes, similar to casein. Moreover, lactalbumin is used to treat stomach ulcer by stimulating mucus secretion, reducing the production of hydrochloric acid, increasing mucin content, and increasing the pH of gastric juice (Matsumoto et al., 2001). This peptide also plays a crucial role in fighting stress due to its high content of tryptophan, the precursor of serotonin, and in lowering blood cortisol level. It regulates blood vessel pressure without affecting cardiac work, and by influencing opioid receptors, like casein, it blocks the activity of the angiotensin converting enzyme. Lactalbumin is able to induce cancer cell apoptosis, thus preventing the disease from developing (Markus et al., 2000).

Conclusions

The data presented suggest that colostrum, and the proteins and peptides isolated from it, can find a number of applications in the prevention and treatment of many human diseases. Due to the higher content of bioactive substances in relation to other farm animals, sheep colostrum may be used in the production of natural supplements which enhance the body's immunity and support circulatory system function. In cardiology, considerable attention is now given to the possible use of lactoferrins. The possibility of using colostrum and milk from sheep as a natural source of bioactive substances could help to develop sheep farming in Poland.

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SUMMARY

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