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THE MILK PROTEIN ALLERGY AND ITS GENETIC BACKGROUND IN THE CASE OF GOAT MILK

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Abstract

The main aim of this paper is to summarize the most current knowledge in the field of genetic polymorhism of the main caprine milk protein genes, namely: α-lactalbumin, β-lactoglobulin and α_{s1}-, α_{s2}, β- and κ-caseins.

In almost all European countries, the primary utilization of goat is for milk and cheese. During cheese production, the amount and quality of the product are determined primarily by caseins (especially by α_{s1}-casein) from the 6 major milk protein fractions. There are several association studies about polymorhism of milk protein genes and milk traits. We would like to refer these results and give a brief review about the current knowledge of the main caprine milk protein gene structure, as well. These information will be followed by a comparison review with polymorhism of bovine and ovine milk protein genes and their special characteristics about milk protein allergy. In Europe and worldwide, the consumption of cow's milk is dominant, but interest toward the milk of other species is increasing. It has a very important role in the human diet, in spite of that, the number of those stopping its consumption is increasing, the reason for which is the spreading of milk allergy.

Key words: polymorphism, goat, review, allergy

MILK ALLERGY

Based on the average data food allergy affects up to 8% of children and 2% of adults. Milk allergy is responsible for a significant ratio in food allergies. About 3% of the infants born as sensitive to milk proteins but this phenomenon declines to about 1% by the time of adult age. This means that the everyday lives and healthy nutrition of about 300.000 people are rendered by this problem. In addition, it has an effect on the lives of their families, meaning that it represents difficulties for 1 million people in Hungary. This disease cannot be cured, but is endurable by keeping a strict diet and spending significant amount of extra money.

According to the new knowledge of recent years, in those suffering from cow's milk allergy an allergy can form also to the milk of small ruminants

due to so-called cross-reactions. This can be ”treated” only if other conditions are met.
For healthy nutrition, especially in the first decade of our lives, the nutrients of milk are essential. In order to provide the people showing sensitivity (milk allergy) to certain milk protein fractions with the nutrients of milk a method should be developed which eliminates the triggering material of the disease from milk without artificial interaction.
Luckily, the milk protein fractions causing allergic reactions (αs1 casein, αs2 casein, β casein, and β lactoglobulin) consist of numerous variants and not all of the variants trigger such a reaction. The different variants can be separated by DNA tests. This enables us to aim for the natural production (without artificial interaction) of products which does not contain these fractions causing allergy. For this purpose, we can select those goats and sheep which produce milk with the required composition and can produce products which can be consumed by those allergic to milk without any negative consequence.

MILK PROTEIN ALLERGY

Numerous articles and news without any scientific background were published in journals and magazines worldwide about the favourable dietary and health-improving effects of goat milk, but very few scientific studies are published in this topic. Beck in his book in 1989 describes 54 Australian cases about the favourable effects of goat milk, but no other similar summarizing study was published although several international scientific journals publish papers in this theme.

The exploitation of the dietary and physiological advantages of goat milk is closely related to the nutrition-health problems of people. Allergy to cow milk changes with age and location, there are no exact data about its frequency, because it is hard to compare the results of the different diagnostic, analytical methods (Kaiser, 1990).

In Europe and worldwide, the consumption of cow milk is dominant, but interest toward the milk of other species is increasing. It has a very important role in the human diet, in spite of that, the number of those stopping its consumption is increasing, the reason for which is the spreading of milk allergy. Allergy is caused mainly by the protein in milk, but in certain people lactose causes digestion problems (lactose intolerance), which is not allergy. The allergenic effect of α_{s1}-casein, α-lactalbumin and β-lactogloulin of cow’s milk has been known for years (Sieber, 2000). The goat milk, the sheep milk and products are not recommended to be consumed for the cow milk allergic patients by reason of strong cross reaction between the milk of different animals (Polgár and Hajós 2000). However, researchers have not reached a consensus whether this product can be replaced by the milk of other animal species for those suffering from cow milk allergy. Some researchers suggest giving goat and sheep milk to children only after the age of 2, while others recommend its consumption already in infancy. With the reduction of cow milk consumption, other alternatives are considered in addition to goat and sheep milk such as soy milk and casein and whey products. According to British research results goat milk is suitable for treating allergy and other cases such as malabsorption syndrome, especially during childhood (McCullough, 2003). However, in France it was found that neither goat nor sheep milk were suitable for replacing cow milk for allergic patients as in certain cases a life-dangering anaphylactic shock can occur. For children suffering from allergy they do not suggest the consumption of these two milk types, while certain patients tolerate donkey, camel and horse milk better. The greatest problem (regarding milk allergy) is that food industry uses an increasing amount of goat and sheep milk and their products in different semi-finished products which can be dangerous for people allergic to them (Moneret-Vautrin, 2004). Compared with cow's milk, goat milk contains less α_{s1}-casein, but more α_{s2}- and β-casein, while ewe's milk contains more of all three proteins than cow milk (Spuergin et al., 1997). Bernard et al. (1999) found 87 and 97.4% similarity between the amino acid composition of cow and ewe milk and goat and sheep milk, respectively.

About 2.5% of the children under the age of 3 suffer from cow milk allergy worldwide, but this value is 7-8 % in Scandinavia (Host et al., 1988), while Nestle (1987) reports about ratios higher than 20% in certain areas. According to Haenlein (2004), treatment with goat milk can solve 30-40% of these cases. In 85% of the cow milk allergy cases polysensitivity was detected for caseins and lactoserum proteins such as α-lactalbumin, β-lactoglobulin (Bernard et al., 1998). The complexity of cow milk allergy is caused by the genetic polymorphism of caseins and whey proteins; therefore, it is hard to state which protein fraction is responsible for the allergic reactions (Grosclaude, 1995). Out of the 18 protein fractions of cow milk, β-lactoglobulin cannot be found in human milk; therefore, it is assumed that this is the most harmful regarding allergy, although the comparative examinations of Buergin-Wolff et al. (1980) and Taylor (1986) did not found a significant difference in the allergenic effect of β-lactoglobulin and casein of cow milk. According to the results of

Kaiser (1990), in skin prock-tests, α-lactalbumin caused the most positive skin reactions for on 21 adult and 13 infant patients with cow milk allergy.

According to Marletta et al. (2005), the allergic effect of 3 casein fractions (homozygous normal, homozygous 0 and heterozygous normal) was similar. Based on the amount of samples, three levels (C_{20}, C_{50}, and C_{80}) were created, according to the % α_{s2}-casein and seroprotein content of the sample. In the case of C_{50}, the most allergenic was homozygous normal followed by homozygous 0 and heterozygous normal. Based on our results, protein fractions have a much greater role in allergic reactions than seroproteins and the lack or low-level of α_{s2}-casein reduces the allergic effect only slightly.

Cross-reactions between the caseins of cow milk and goat milk are well-known, but according to Paty et al. (2003) numerous cross-reactions can occur also between goat and sheep milk. When a goat milk-specific IgE is present, the radioallergosorbent test (RAST) shows positive result for sheep milk. The main allergens were found to be α_{s1}- and β-casein in both goat and sheep milk. On the other hand, the not totally identical amino acid sequence of caseins can be the reason why allergic reactions can occur during the consumption of goat and sheep milk in people not allergic to cow milk.

Based on the results, the authors concluded that milk types can be differentiated according to the protein fractions determined by the different alleles and the causes of allergy can be prevented in a natural way.

In Hungary, a limited number of studies were performed on goat milk allergy, but no studies have been done in relation to sheep milk.

PROBLEM OF MILK COMPOSITION

Milk and dairy products have always been important in human nutrition, consequently, they served as a basis of animal breeding and genetic research at an early stage. Via traditional breeding methods, the amount of milk produced was significantly increased; however, this was frequently accompanied by a deterioration of inner content parameters. For selecting the individuals producing milk with favourable composition, the methods of molecular genetics are of great assistance. The milk protein genes of important milk-producing domestic animal species were isolated and the genetic variants influencing milk quality were described. In Hungary, the demand for goat and ewe's milk and their dairy products is not high; however, the consumers are willing to pay a high price for them in France and Slovenia. Medical research has proved that goat milk and its dairy products have a very favourable physiological impact. Goat milk is the healthiest one of all milk types; its vitamin content is much higher than that of cow's milk. It can be digested easily and tastes good; therefore, it has an important role in the diet of those suffering from stomach and digestion problems and is excellent for the elderly due to its high protein content. Due to its favourable calcium-phosphorus ratio, osteoporosis can be prevented via its regular consumption. It has been well-known about ewe's milk that it does not cause allergy. In recent publications, however, the basis of this information has been shaken: it can occur that an allergic reaction does not form to cow's milk, but it occurs for sheep (and goat) milk.

The milk composition of the two small ruminant species was studied by several authors in the last decades. They found that variety and feeding have an impact on milk composition. So far, it has not been studied how the keeping technology affects milk composition (e.g. vitamin D and Ca contents). Studies on cow's milk production showed that intensive and extensive (only grazing) and semi-intensive keeping technologies do not only modify the mineral matter and vitamin content, but also the macro- and microcomposition of milk. This is completely non-clarified for sheep and goat milk. Dixit et al. (2012) found in silico analysis of alpha s1-, alpha s2-, beta- and kappa-caseins and beta-lactoglobulin, unveils that sheep milk is a more suitable alternate to cow milk for allergic infants and buffalo milk for allergic adult humans.

According to an other study there was no significant difference between goat and sheep alpha S1 and S2 proteins, thus both have the same properties and useful alternative for the cow milk allergic children (Masoodi and Shafi, 2010).

COMPOSITION OF GOAT MILK

In almost all European countries, the primary utilization of goat is for milk and cheese. During cheese production, the amount and quality of the product are determined primarily by caseins (especially by α_{s1}-casein) from the 6 major milk protein fractions.

In 1984, Boulanger et al. identified 7 different α_{s1}-casein variants (alleles). Later, it was realized that the genetic variants can be classified according to their amount in goat milk and the "high", "medium" and "low" variant groups were created (Grosclaude et al., 1987). Accordingly, as the amount of α_{s1}-casein is around 3.6 g/l in the milk of goats with A, B and C variants, therefore, they belong to the "high" group, while variant E (1.6 g/l) and variants D and F (0.6 g/l) were classified into the "medium" and "low" groups, respectively. According to the authors, all variants play an important role in influencing the synthesis of α_{s1}-casein. At the end of the 1990s, three further genetic variants of α_{s1}-casein were identified (Martin and Addeo, 1996). The presence of variant G, similarly to variants D and F was found to be low, and 3 subvariants of B were found: B_1, B_2, B_3, which are synthetised in a relatively high amount. Consequently, 55 different allele combinations are possible in goats. Some authors consider null variants as a fourth group. Clark and Sherbon (2000) described 22 combinations of 10 α_{s1}-casein genetic variants /A, B_1, B_2, B_3, C, D, E, F, G, and 0 (zero)/ in an American goat stock of 93 animals. The combination F/F was found to be the most frequent (37.6%). F/E and E/E represented 10.8%, while only 4.3% of the goats were 0/0 homozygous for α_{s1}-casein. In all the other homo- and heterozygous combinations, only ”high” variants were found, but in a very low frequency (e.g. A/A 2.2%, C/A 1.1%). According to our examinations, F (54.1 and 45.5%) and E (20.3 and 31.9%) are prevalent in the varieties alpine and Saanen, F dominates (41.7%), while E is missing and A is the second most significant (25%) for Nubian. The frequency of the other variants ranges between 1.4 and 6.8 for alpine and 4.6 and 9.1 for Saanen, but variants C, D and 0 were missing. The authors compared their results with those of earlier studies by others and found that the frequency of α_{s1}-casein variants in American goats (Alpine and Saanen) is similar to those examined in France and Italy. The most important difference was found in the frequency of variant E, which was 18.8% in their study, while the Italian and French researchers found it to be 30-40% (Clark and Sherbon, 2000).

Numerous researchers focused on mapping the relationships between casein types and milk composition. Goat milk with high α_{s1}-casein content was found to have better milk composition including fat, protein, casein and phosphorus content and lower pH (Clark and Sherbon, 2000). In addition, the coagulation time of goat milk with high α_{s1}-casein content is longer, but the coagulation level is quicker and the resulting congealment is more solid compared with goat milk of low α_{s1}-casein content (Clark and Sherbon, 2000). According to Ryniewicz et al. (1996), the protein, casein and soluble solid contents are higher, the quality of the congealment is better in goat milk with ”high” variant α_{s1}-casein content. Manfredi et al. (1993), Remeuf (1993) and Barbirei et al. (1995) came to similar conclusions regarding casein content, total protein and milk fat contents. In goat milk with A/A type α_{s1}-casein content, nitrogen and fat content is higher than in the 0/0 type (Pierre et al., 1996). From the A/A type milk, more and more solid cheese can be produced and the goat-smell is less detectable. Aleandri et al. (1990) suggested that during the selection of goat, genetic combination should be considered for optimal cheese production and higher fat and protein content. For profitable production, it is very important to know which α_{s1}-casein genetic variants are responsible for better milk composition and coagulation characteristics. Jordana et al. (1996) studied the α_{s1}-casein content and variants in the milk of 4 Spanish goat varieties. An other study found that Norwegian Dairy Goats have extremely high frequency of an αs1-casein "null" allele (Devold et al., 2010). For the three continental goat varieties (Murciana-granadina, Malaguena and Payoya) variant E was found to be prevalent (60-75%)."High" type variants (A, B, C) ranged between 18 and 31%, while the "low" type (F,D) and 0 variants were present at a maximum of 17%. F, D and 0 variants could not be detected in the milk of the payoya variety. Differences were found between the 3 subtypes of the fourth variety, Canaria goat and between Canaria and continental goats. For this variety, "high" type variants were dominant, at 60% on average. The same variants (A, B) were found in a similarly high ratio in Italian Garganica and Maltese varieties by Ramunno et al. (1991). Variant E in Canaria variety (Jordana, 1996) ranged between 9 and 32% only. Grosclaude et al. (1995) concluded that the frequency of "high" type variants is low, not only in the Alpine and Saanen varieties with strong selection for milk production, but also in unselected, isolated goat varieties such as Corsican goat. However, contradictory results were found in local varieties such as Canaria or Garganica, where the frequency of "high" type variants was high. Based on these results, it seems that selection for milk quantity has a strong effect on the distribution of α_{s1}-casein variants in goat milk. Clark and Sherbon (2000) found the lowest amounts of all milk constituents in the milk of 0/0 animals, while the amount of fat, protein, fat-free soluble solids and total soluble solids was the highest in milk containing "high" type α_{s1}-casein variants. They claimed that the "medium" type E variant is the one improving milk composition, but the difference between the milk composition of E and 0 variants was not significant. There was no significant difference in the coagulation characteristics of milk samples from animals with different variants and combinations, but a strong trend could be observed according to which both the coagulation time and firmness of the congealment were lower in milk with 0/0 α_{s1}-casein genetic variants than those of the other types (low, medium and high) of milk. According to their conclusions, goats of /0 α_{s1}-casein genetic variant should be removed from the stock by selection and goats inheriting A, B_1, B_2, B_3 and C variants and their combinations should be bred further, if we aim to improve milk composition and to increase cheese production. Another suggested solution is the thorough selection of the variety, as the milk of Nubian variety contains significantly more ”high” type variants than those of Alpine or Saanen goats (Clark and Sherbon, 2000). In the study of Addeo et al. (1989), goat milk not containing α_{s1}-casein was more sensitive to ethanol and heat and its coagulation time was prolonged and the resulting congealment was softer. In France, goats with A, B and C alleles produced significantly less milk, but more casein and the congealment produced from their milk was more firm than goats with B and 0 genotype (Remeuf, 1989).

In Hungary, at the Agricultural Biotechnology Center in collaboration with co-workers of the University of Debrecen and the Research Institute for Animal Breeding and Nutrition (Herceghalom) goat milk casein fraction model studies were performed using Hungarian milking goat stocks. The frequency values of α_{s1}-casein obtained for Hungarian milking goats were significantly different from those published in the international literature (Veress et al., 2004; Kusza et al., 2007).

The two variants of αs2-casein (A and B) were analysed first by Boulanger et al. (1984). With the technical development, the analytical methods became more precise, and variant C was detected by Bouniol et al. in 1994. 7 αs2-casein alleles were found in goat, which are classified into three groups based on the αs2-casein content of milk. The αs2-casein content (about 2.5 g/l) is missing, reduced and normal in the case of 0 (Ramunno et al., 2001b), D (Ramunno et al., 2001a), and all the other known alleles (A, B, C, E, F) (Bouniol et al., 1994; Lagonigro et al., 2003), respectively.

According to Ramunno et al. (2001b), the 0 allele has a significant effect on goat milk composition, as the ”normal variant” and the heterozygous normal gave only 16% and 9% of the total casein, respectively.

The presence of allele 0 is relatively high in the Hungarian milking goat stock as compared to other European varieties (Kusza et al., 2007).

According to Moioli et al. (1998) β-casein is one of the most important casein fractions in goat milk, in spite of that, the firs publication about it was only in 1989. Using the polyacryl-amid gel-electrophoresis method, Ramunno et al. 1995 detected β-casein in local Italian goats and then they also found the 0 variant in Corsican goats. Examining cow, buffalo, sheep and goat milk, Iranian researchers found that the highest and lowest amount of proteins can be found in sheep and goat milk, respectively, the highest amount of β-casein was found in goat milk, but this was accompanied with the lowest α-casein content.

The significance of κ-casein is in the formation and stabilization of micelles. In cheese production, the peptide bounds between phenyl-alanine and metionine are broken. Based on existing studies A+B allele and C allele are differentiated. According to Spanish researchers allele C has a high frequency in Saanen stock selected for milk production, while its ratio is low or it is missing in other varieties. The frequency of κ-casein alleles in Hungarian stocks is very similar to that of the French Saanen stock (Veress et al., 2004). According to other Spanish examinations, B homozygous goats produce significantly more milk with higher casein content than those of the other two genotypes (Angulo et al., 1994).

CONCLUSIONS

Nowadays there are several project which aims at the technological development of less allergenic food products based on sheep and goat milk containing allergens that are highly potent and stable and do not trigger allergic effects and at improving food safety by strategies to prevent allergen contamination. The approach includes development of sensitive and reliable allergen detection methods and allergenic assessment of foods containing animal milk. DNA based methods for allergen determination in foods are applied, introduced and developed.

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