Recent advances in exploiting goat's milk: quality, safety and production aspects

N. Silanikove [a,*], G. Leitner[b], U. Merin[c], C.G. Prosser[d]

[a] *Biology of Lactation Laboratory, Institute of Animal Science, Agricultural Research Organization, The Volcani Center, P.O. Box 6, Bet Dagan 50250, Israel.*

[b] *National Mastitis Reference Center, Kimron Veterinary Institute, P.O. Box 12, Bet Dagan 50250, Israel*

[c] *Department of Food Science, Agricultural Research Organization, The Volcani Center, P.O. Box 6, Bet Dagan 50250, Israel*

[d]*Dairy Goat Co-operative (N.Z.) Ltd., Hamilton, New Zealand*

* Corresponding author: Tel: +972 8 9484436, Fax: + 972 8 9475075.

E-mail address: nsilamik@agri.huji.ac.il (N. Silanikove)

Abstract

Goat milk production is a dynamic and growing industry that is fundamental to the wellbeing of hundred of millions of people worldwide and is an important part of the economy in many countries. The aim of the present review is to provide an integrated and critical analysis of the major aspects in this field to highlight unexploited nutritional potential of goat milk and the need for improvements, particularly in food-safety. First, it should be kept in mind that goat milk like cow milk delivers many nutrients with relatively low energy content, and is relevant to the health of consumers throughout the life cycle. In addition, our review presents data suggesting that goat milk possesses many advantages over cow's milk, for use as a nutritional source for infants and children and as a medicinal food. Furthermore, we suggest that goats, by consuming large amounts of natural browsing plants all year around, is a potentially overlooked "treasure trove", with respect to health promoting components. Our survey suggests that total bacterial count that is currently used as the major quality measure to prevent pathogen-related food toxiciosis in Europe and the USA is not sufficiently effective. We propose the inclusion of somatic cells count as a routine criterion to qualify the hygienic status of goat milk, and discuss the physiological and biochemical basis for this. Finally, we present a novel mechanism controlling milk secretion, and demonstrate the use of this knowledge in making decisions for two major managemental tasks that farmers face: i) Milking frequency that dictates to large extent the milk yield and workload in the farm, and ii) Helping to deal with subclinical mastitis, which is the single major cause for economical losses in dairy farms worldwide.

1. Introduction

Herding of goats is thought to have evolved about 10,000 years ago in the mountains of Iran, making goats one of the oldest domesticated animals (Haenlein, 2007). Goat milk, and the cheese made from it, were venerated in ancient Egypt with some Pharaohs supposedly having these foods placed among the other treasures in their burial tombs (Smith, 2006). Goat milk continued to play an important role in human nutrition in areas acknowledged as the cradle of modern civilization (Hatziminaoglou and Boyazoglu, 2004).

It is estimated that over 80% of the world's goat population is located in Asia and Africa (Morand-Fehr et al., 2004). Thus, in fact, more people in the world drink milk from goats than from any other animal. What makes goats so popular is their ability to provide high-quality food under diverse climatic conditions and resilience to extreme and capricious environments (Silanikove, 1994, 2000).

In regions such as Europe, Oceania and North and South America dairy production from goats has become more of a commercialized operation, For example, cheese production is a significant industry in countries such as France and Italy, where goat cheese is regarded as a gourmet food and receives the highest prices among cheese varieties in the market. In addition, dairy goat and dairy sheep farming are a traditional and fundamental part of the national economy in many Mediterranean countries, such as, Spain, Greece, Turkey and Morocco (Park et al., 2007). A more detailed examination of the goat industry and production system in different parts of the world is provided in the review by Dubeuf (2005).

New markets and uses for goat milk are also being pursued, for example as a basis for medicinal and infant foods. .With the growing interest in existing and new goat dairy products world-wide it is imperative that quality and safety of goat milk are optimized

to ensure consumer confidence. The aim of this publication is to review recent advances in goat milk quality, safety and production in respect to its use in the food industry. A special emphasis will be placed on the advantages of goat milk for developing new niche markets. In the production section, we present a novel mechanism controlling milk secretion in goats. The use of this knowledge in making decisions regarding milking frequency in goat farms and in dealing with subclinical mammary infections will be discussed.

2. **Basic and unique features of the composition of goat milk**

Research in the 20th century has led to a substantial increase in our knowledge of the basic and unique features of the composition of goat milk. This aspect was covered most recently by Park et al. (2007) and Haenlein (2004, 2007). Thus, we will only briefly summarize the main points, important for the rest of this review.

2.1. Lipids of goat milk

The percentage of total fat in goat and cow milk is quite similar, and the fatty acid composition depends to a large extent on the diet composition in both species. Two characteristics of goat milk fat have important consequences for manufacturing. One is the smaller size of the fat globules in goat milk in comparison to those in cow milk. In both species the fat globules range from 1 to 10 μm, but the number of fat globules less than 5 μm is ~60% in cow milk whereas it is ~80% in goat milk. This difference results in a softer texture of goat milk products, though it makes manufacture of butter from goat milk difficult. The second feature, is the fatty acid composition of goat milk with a higher proportion of medium chain fatty acids, i.e., caproic (C6:0), caprylic (C8:0) and

capric (C10:0), which are partly responsible for the characteristic "goaty" odour of goat milk.

2.2. Carbohydrates in goat milk

As in cows, lactose constitutes the main carbohydrate in goat milk. Goat milk does contain less lactose than cow milk (on average, 4.1% vs. 4.7%), but can not be regarded as a dietary solution to peoples suffering from lactose intolerance.

2.3. Proteins of goat milk

Cow milk and goat milk do not differ significantly as far as the protein percentage is concerned and, in contrast to milk fat, the protein content in both species is less amenable to dietary manipulation.

However, casein micelles in cow milk are small (60-80 nm) when compared to goat milk casein micelles, which range between 100-200 nm. Another key difference between species is the level of α_{s1}-casein. The level of α_{s1}-casein in goat milk ranges from 0-7 g/L (Martin et al., 2002). This variability is associated with polymorphisms within the alpha s_1-casein gene, which are very common in goats (Martin et al., 2002). The importance of this characteristic will be discussed later.

2.4. Minerals and vitamins

The mineral content of goat milk varies from 0.70 to 0.85%, and compared to human and cow milk, goat milk contains more calcium, phosphorous and potassium. The vitamin content of goat milk is similar to that of cow and human milk.

3. Use of goat milk in developing functional (medicinal) foods

Traditionally, goat and cow milk has been considered as a fundamental food in the diets of many cultures. Milk provides an easily accessible matrix, rich in a large variety of essential nutrients like minerals, vitamins and easy digestible proteins with balanced amino acid profiles, important in supporting most body functions. Together with grains, meats, vegetables and fruits, dairy products are categorized as nutrient-dense foods, i.e., foods that deliver many nutrients with relatively low energy content, and are relevant to health throughout the life cycle (Drewnowski and Fulgoni, 2008).

Consumption of dairy products and goat milk in particular, is also associated with beneficial health effects beyond its pure nutritional value. Dairy products also serve as vehicles for other functional ingredients, such as phytosterols (as cholesterol replacement), fish fatty acids (as omega-3 acids) and various kinds of probiotic bacteria (e.g., Mattila-Sandholm et al., 2002). Whilst this subject exceeds the scope of this review and will not be considered further, the next section discusses those aspects of goat milk that make it an excellent matrix for developing a large variety of innovative health promoting products or functional foods.

3.1. Gross composition

In addition to contributing to the specific "goaty" flavor, the higher proportion of medium chain fatty acids in goat milk, are known to: i) be anti-bacterial, ii) be anti-viral, iii) inhibit development and to dissolve cholesterol deposits, and iv) be absorbed rapidly from the intestine (Shingfield et al., 2008). Thus, these characteristic undoubtedly contribute to the specific health promoting properties of goat milk. However, further research is needed to exploit these interesting characteristics of goat milk in full.

As human milk lacks α_{s1}-casein, the low levels of α_{s1}-casein in some goat milks and higher proportion of β-casein means that goat milk casein profile is closer to human milk than that of cow milk (Clark and Sherbon, 2000). Bevilacqua et al. (2001) noted that contradictory results that have been reported on the use of goat milk in cow milk allergy could be due to the high genetic polymorphism of goat milk proteins, particularly, α_{s1}-casein. These authors found that guinea pigs fed goat milk with low α_{s1}-casein produced significantly less antibodies to β-lactoglobulin than animals fed with goat milk containing higher α_{s1}-casein. They suggested that the digestion of β-lactoglobulin was enhanced by the relative absence of α_{s1}-casein

Goat milk is reported to form a finer curd than cow milk following acidification, which mimics the conditions in the stomach, suggesting it would be more readily digested (Park, 2007). In vitro studies confirm a different pattern of digestion of goat milk proteins compared to cow milk proteins. For example, Jasińska (1995) showed that 96% of goat casein was completely hydrolysed in vitro by trypsin compared with and only 76-90% of cow's casein. Similarly, goat milk was degraded significantly faster by human gastric and duodenal juices than cow milk (Almaas et al., 2006).

3.2. The composition of minor components in goat milk

In comparison to the differences in gross composition between goats and cows, those related to the minor components, such as the oligosaccharide and non-protein nitrogen fraction, are more pronounced. Although present at low concentrations, these components can have a profound impact on the development and maintenance of metabolic, immunological and physiological processes and thus contributes some of the key advantages of goat milk in developing nutritional products.

3.2.1. Amino acids

Goat milk contains a similar amino acid profile to cow milk and, except for a lower concentration of cysteine, to human milk as well (Rutherfurd et al., 2008). However, concentrations of methionine and cysteine, when added together, are equivalent in goat and human milk protein (Rutherfurd et al., 2008). Milk also contains a range of free amino acids that may be utilized directly by the intestine (Duggan et al., 2002). In goat milk, taurine, glycine and glutamic acid are the major free amino acids (Rutherfurd et al., 2008).

Taurine is particularly high in goat milk, being 20-40-fold higher than cow milk (Mehaia and Al-Kanhal, 1992). Taurine is involved in bile salt formation, osmoregulation, antioxidation, calcium transport and in the central nervous system (Redmond et al., 1998). Premature infants who lack the enzymes needed to convert cystathionine to cysteine may become deficient in taurine. Thus, taurine is a dietary essential nutrient in these individuals and is often added to many infant formulas as a measure of prudence (Bouckenooghe et al., 2006). Taurine is also beneficial for adults, helping to regulate blood pressure and possibly to alleviate other cardiovascular ailments (Militante and Lombardini, 2002). Taurine is often used in combination with performance enhancing substances, such as creatine and anabolic steroids, partly due to recent findings in mice that taurine alleviates muscle fatigue in strenuous workouts and raises exercise capacity (Warskulat et al., 2004). Thus, goat milk is a valuable source of taurine for the human neonate and the adult, particularly those interested in the exercise-promoting features of taurine.

3.2.2. Other non protein nitrogen components: nucleotides and polyamines

Nucleotides (Nu) are assumed to facilitate immune maturation of the milk-fed offspring and are often added to infant formulas (see Schallera et al., 2007 for review). Nu's are major components of RNA and DNA, and participate in the mediation of energy metabolism, signal transduction and general regulation of cell growth. Nu also participate in lipoprotein metabolism, enhanced high-density lipoprotein (HDL) plasma concentration, as well as enhanced synthesis of apolipoprotein (Apo) A1 and Apo A1V in preterm infants, and in upregulation of long-chain polyunsaturated fatty acid synthesis in human neonates (Schallera et al., 2007). Ribonucleotides (RNu) are considered 'conditionally essential' for the proper development of human neonates, because the supply of RNu through *de novo* synthesis and endogenous salvage pathways is thought to be insufficient for optimal functioning of rapidly growing intestinal and lymphoid tissues, even though their low levels might not result in an overt clinical deficiency (Schallera et al., 2007). RNu have been extensively studied as ingredients in infant formulas and several reviews for such a role have been published (see Schallera et al., 2007 for review). One of the main reasons driving development of infant formulas enriched in Nu is the high amounts in human milk (Schallera et al., 2007). Goat milk, differently from cow milk, also contains a complex array of Nu (Prosser et al., 2008). The Nu content of infant formula made from goat milk approaches the same levels as human milk without the need for additional Nu (Prosser et al., 2008).

Polyamines, another component of the non-protein fraction of milk was shown to be important for optimal growth, gastro intestinal tract (GIT) cell function, maturation of GIT enzymes (Pegg and McCann, 1982) and have been implicated in reducing the incidence of food allergy in infants (Dandrifosse et al., 2000). Ploszaj et al. (1997)

found that goat colostrum and milk are rich in polyamines, being the highest compared to milk of other mammals (e.g., human, rat, sow, and cow). Prosser et al. (2008) found that goat milk and goat-based infant and follow-on formulas were marginally richer in polyamines content than cow milk or cow milk-based formulas; though in both species the levels are much lower than in human milk.

In summary, goat milk appears to be an excellent source of Nu for infant and follow-on formulas and has the potential to be a good source of polyamines. The content and availability of Nu and RNu most likely depend on the activity of an array of related milk enzymes (Silanikove, 2008), but virtually nothing is known about their presence and function in goat milk. Further research is also needed to distinguish between DNA-derived Nu and RNu, and the potential nutritional benefits of nucleosides and polyamines in goat milk.

3.2.3. Oligosaccharides

Oligosaccharides are considered to be beneficial components of human milk due to their prebiotic and anti-infective properties (Boehm and Stahl, 2007). These compounds function as scavenger receptors for various pathogens, as an inhibitor of *Escherichia Coli* heat-stable enterotoxin and in blocking leukocyte-endothelial cell interaction, thus serving an anti-inflammatory function (Boehm and Stahl, 2007). The fact that most oligosaccharides (> 95%) from human milk are resistant to digestion suggest that their main target of biological functions is the GIT of the neonate. Only fructo- and galacto-oligosaccharides are commercially available for adding to formulas. These relatively simple structured oligosaccharides possess a prebiotic effect, such as stimulation of GIT Bifidobacteria and Lactobacilli (Boehm et al., 2002), but lack the other important anti-infective functions of oligosaccharides (Boehm and Stahl, 2007).

Recently, oligosaccharides from goat milk were characterized (Viverge et al., 2007) and quantified (Martinez-Ferez et al., 2005). Goat milk typically contain between 250 to 300 mg/L oligosaccharides, 4-5 times higher than the content in cow milk and 10 times higher than that of sheep milk, but still much lower than in human milk, at 5 to 8 g/L. The oligosaccharides in goat milk are complex, with a profile most similar to human milk, in comparison to cows and sheep. Oligosaccharides have been isolated from goat milk in high yield (Martinez-Ferez et al., 2005) and shown to be anti-inflammatory in a rat model of hapten-induced colitis (Daddaoua et al., 2006) and dextran sodium sulfate-induced colitis (Lara-Villoslada et al., 2006). Thus, goat milk appears to be an attractive natural source of human-like oligosaccharides for infant and follow-on, and health-promoting formulas, due to its composition and content.

3.2.4. Effect of browse in the diet of goats on the composition of minor milk components: are we overlooking a "treasure trove"?

Fodder trees, fodder shrubs and herbaceous species are very important sources of food for livestock, particularly in desert and semi-desert regions (Silanikove, 2000; Silanikove et al., 2001). Most browse species are dicotyledons that contain large amounts (up to 50% of the dry matter) of polyphenols, many of them tanniferous compounds (Silanikove et al., 2001). Unlike sheep and cattle, which predominantly select leafy material during spring, browse constitutes 50% to 80% of the forage selected by goats all year round. It was suggested that this behavior is an adaptive mechanism that allows goats to maintain a high intake of browse to preserve their specific superior capacity in utilizing food rich in tannins and other source of secondary metabolites (Silanikove, 2000).

In general, milk produced from pasture based farming systems with adequate nutritional quality is characterized by high fat content, because of the fiber-rich forages (Morand-Fehr et al., 2007). In addition, the studies outlined below demonstrates that these milks are also rich in micro-components (fatty acids, vitamins) and in volatile compounds (flavours, terpenes), and phenolic compounds, favorable to human nutrition and health.

3.2.4.1. Effect of fat soluble vitamins, unsaturated fatty acids and conjugated linoleic acid (CLA) content in milk

As mentioned previously, the higher quantity of medium-chain fatty acids characteristic of goat milk, presents several advantages for consumer health. There is a large body of evidence indicating that forage species, particularly the proportion of leguminous forage in the diet, can also significantly affect fatty acid composition and bioactive lipids components in ruminant milk (Shingfield et al., 2008). Thus, additional advantages in respect to the health promoting lipids in goat milk can be attributed to their specific food selection habits and the interaction between dietary components and the digestive system (Chilliard and Ferlay, 2004; Shingfield et al., 2008). A French study demonstrated that pasture-based rations rather than the hay-based rations for goats were associated with higher levels of xanthophyll, retinol, α-tocopherol in Rocamadour cheese (Lucas et al., 2008). Higher proportion of concentrates in the diet led to lower xanthophyll and α-tocopherol contents. The vitamin supplementation of hay-based rations, unlike that of pasture-based rations, was associated with higher levels of retinol but not of α-tocopherol in cheese fat. This study has shown that the nature of the basic fodder ration is the main factor influencing retinol, α-tocopherol and xanthophyll

contents of Rocamadour cheese and thus, most likely, the milk used to produce it (Sanz Sampelayo et al., 2007).

Another milk factor of interest is conjugated linoleic acid (CLA). Studies have show that dietary CLA can reduce oxidative stress, atherosclerosis and improve blood lipids profile, in addition to conferring protection against the growth of tumors of mammary gland and skin (Chilliard and Ferlay, 2004; Shingfield et al., 2008). This has lead to efforts to increase the CLA content of domestic ruminant milks, but so far this research has not yielded a commercial product, most likely because the cost of the dietary source for CLA is high, and because the resulting enrichment in CLA content in milk was modest.

In an Italian study, milk of goats grazing pasture composed of Leguminosae (*Trifolium alexandrinum*, *Vicia* spp.) and 40% grasses had significantly higher fat content than milk from hay-fed control animals (Decandia et al., cited in Morand-Fehr et al., 2007). Among milk fatty acids, pasture significantly affected the percentages of C18:1 *cis*-9, C18:1 *trans*-11 (CLA), octadecadienoic acid, mono-unsaturated fatty acids and polyunsaturated fatty acids. Studies in Greece (Tsiplakou et al., 2007) and Mexico (Galina et al., 2007) were carried out with goats grazing on a typical scrubland pastures. Both studies has shown that milk and cheese from grazing animals was better in quality parameters for human nutrition than that produced from milk of indoor fed animals. As in the Italian study, Tsiplakou et al. (2007) showed that the concentration of the cis-9, trans-11 isomer of CLA increased in milk fat from pasture fed goats, in association with significant reduction in the atherogenic index of the fatty acids. A negative relationship between milk fat and *cis*-9, *trans*-11 CLA level was found only in sheep in that study. The authors suggested that sheep milk is richer in CLA than goat milk. However, pasture for sheep differed considerably from pasture for goats and differences in milk

yield were not taken into account. Reanalysis of the data of Tsiplakou and Zervas (2008) demonstrates the importance of accounting for difference in genetics between species: in this study intake of 751 and 702 g/kg dry matter of olive tree leaves in sheep and goats and intake of 196 and 189 g/kg dry matter grape marc resulted in an increase of 1.5 g/day in secretion of *cis*-9, *trans*-11 CLA level in the former case and 0.5 in the case of grape marc, in both species. Thus, the data indicate essentially similar biological efficiency in converting linolenic and linoleic acids in these dietary sources into milk *cis*-9, *trans*-11 CLA, and the differences in their content in milk fat, merely represent species differences in milk fat content and milk yield.

In conclusion, several studies have shown that milk of goats on pasture is naturally enriched in fat soluble vitamins, unsaturated fatty acids and CLA, in addition to being naturally rich in medium-chain fatty acids. Furthermore, goats on pasture have an improved profile of medium-chain fatty acids, in comparison to goats fed conventional concentrate-forage diets (Kondyli and Katsiari, 2002); high-alpine pasture was shown to be more effective than low-land alpine pasture in this regard (Žan et al., 2006). Thus, milk from goats feeding on pasture may present an overlooked "treasure trove" with respects to its health promoting lipid profile. Nevertheless, further research in various pastoral environments is needed to fully exploit the health promoting potential of goat milk lipids. Given free choice, it is highly likely that voluntary consumption of browse material like olive tree leaves would be higher in goats than in sheep, re-emphasizing our null hypothesize that the main advantage of goats over other ruminant species in producing milk rich in valuable nutritional sources relates to its unique feeding habit and high digestion capabilities. However, a deeper understanding of the interactions between lipids and non-lipid components of pasture and milk composition is needed (Chilliard and Ferlay, 2004; Shingfield et al., 2008).

3.2.4.2. Occurrence of plant secondary metabolites in goat milk

Plants produce an enormous array of secondary metabolites, which serves diverse functions, such as protection against microbial pathogens, as a natural deterrent to grazing animals, or as inhibitors of pre-harvest seed germination (Silanikove et al., 2001). Tannins are the prevailing secondary metabolites when considering the diets of ruminants.

Local goat breeds of the Mediterranean basin have been adapted to the Mediterranean scrubland, consisting mostly of high-tannin containing plants (Silanikove et al., 2001), for over than 7000 years. These goats are able to consume as much as 10 g/day of hydrolysable tannins and 100-150 g/day of condensed tannins without evidence of toxicity (Silanikove et al., 1996). This ability to ingest tannins exceeds the capacity of sheep and cattle, which indeed are not able to survive without considerable supplementation on such grazing land (Silanikove, 2000; Silanikove et al., 2001). Detoxification of tannins by goats is based on enzymatic hydrolysis and depolymerization of the ingested tannins (Silanikove, et al., 2001). Thus, theoretically, large amount of hydrolysable and condensed tannins-derived phenols as well as of other types of phenolic compounds are absorbed from the GIT by browsing goats.

Studies have shown that the physical, chemical and organoleptic features of milk and cheese are greatly affected by the diet of the grazing animals, due to accumulation of phytochemicals in the lipid and water-soluble fraction of milk (O'Connell and Fox, 2001). In particular, monoterpens were identified as compounds that greatly influence the aroma of milk. The study of milk terepens has progressed to a stage that these compounds can be used as biochemical indicators of the composition of the forage grazed and thus for the authentication of the geographical origin of goat cheese

(Fernandez et al., 2003). Whereas quite a few studies on the impact of diet on the content of monoterpene and sesquiterpene in milk cheese are available (De Feo et al., 2006 and references cited therein), very little is known on the effect of diet on the content of non-volatile phenolic substances in milk or cheese. The results of a few recent studies demonstrate the accumulation of various phenolic compounds in the milk of grazing goats (De Feo et al., 2006; Jordan et al., 2007; Sakakibara et al., 2004). High content of phenols in milk has shown to improve the quality of milk, such as its oxidative stability and the processing efficiency and quality of dairy products (see O'Connell and Fox, 2001, for review). Whereas this proposition is still speculative, in our view, goat milk rich in phenolic compounds derived from the diet represents a 'treasure trove' of potential opportunities for developing functional foods.

3.3. Goat milk and the development of food allergy in consumers

This issue was recently reviewed (El-Agamy, 2007). Therefore, only the key topics and conclusions will be highlighted here.

First, it should be emphasized that allergy towards a given food may be developed, particularly in the first year of life, for any food that is different from the milk of the nursing mother (Noimark and Cox, 2008). Therefore, it is not surprising that allergy that is specific to goat milk has been identified (e.g., Ah-Leung et al., 2006). However, symptoms of allergy to goat milk appeared at a much later age than cow-milk allergy (Ah-Leung et al., 2006), which may benefit younger infants who are dependent on milk as their main source of nutrients. In addition, allergy-related symptoms to goat milk may develop in individuals who have already developed an allergy to cow milk (Bellioni-Businco et al., 1999). However, an average of 5 times more goat milk than cow milk was required to trigger an adverse reaction (Bellioni-Businco et al., 1999)

lending some support for a difference in the allergenic potential of goat and cow milk. Bevilacqua et al. (2001) have suggested that the reduced allergenicity of goat milk might be directly related to the lower levels of α_{s1}-casein.

A study in mice provided preliminary data that goat milk may also be helpful in delaying the development of allergy if introduced immediately following weaning. Only 1 out of 13 mice weaned on to goat milk showed symptoms typical of food allergy whereas 8 of 13 mice become sensitized to cow milk, (Lara-Villoslada et al, 2006). The severity of allergic reactions was almost 3 times greater in mice with allergy to cow milk.

In conclusion, further research and clinical trials will be required to establish whether goat milk may reduce the risk of developing allergy in infants or to identify if goat milk may benefit individuals who have already become sensitized to cow milk proteins or other food allergens. As a general precaution, it is recommended that any new food, including goat milk, should only be introduced into the diet of individuals who are highly reactive to cow milk, particularly infants, in consultation with appropriate medical professionals.

3.4. Nutritional studies with animals and humans applying goat milk or goat milk powder as a major dietary source

Some of the positive features of goat milk as a nutritional media, or as a source of food for nutritional formulas for humans can be intuitively predicted from its composition. However, as we are dealing with a complex media, it will most likely contain other overlooked attributes. The advantage or disadvantage of these may only be revealed through direct nutritional studies using appropriate animal models. In this

section, we will review the relatively limited research done with goat milk and goat milk powder in such animal models and human studies.

Both human and animal studies indicate that goat milk fat is utilised more efficiently than cow milk fat (Hachelaf et al., 1993; Alferez et al., 2001). This feature of goat milk most likely relates to its unique enrichment in medium chain fatty acids. Goat milk powder prevented the loss of intestinal barrier function that follows heat stress in a rat model (Prosser et al., 2004), which may relate to the peculiar lipid profile and the relatively high content of oligosaccharides. Feeding goat milk also increased biliary secretion of cholesterol and a decreased plasma cholesterol levels in rats (Lopez-Aliaga et al., 2005). Growing piglets fed goat milk generally had higher bone mineral density, less body fat and less fat mass than those fed bovine milk (Murry et al., 1999). The greater bone density in the goat milk-fed piglets may have been due to the greater concentrations of plasma minerals, reflecting a better uptake of minerals.

Milk in general is considered a high quality dietary source of calcium. In earlier studies, it has been shown that goat milk can benefit growth and skeletal mineralisation in children (Hachelaf et al., 1993; Razafindrakoto et al., 1994). Furthermore, greater uptake of calcium and higher calcium content of femur, sternum and longissimus dorsi muscle was noted in rats following consumption of goat milk compared to cow milk (Lopez-Aliaga et al., 2000; Campos et al., 2003; Kruger et al., 2008). In other rat studies, goat milk also benefited uptake and utilisation of iron (Park et al., 1986; Lopez-Aliaga et al., 2000; Barrionuevo et al., 2002; Alferez et al., 2006), copper (Barrionuevo et al., 2002), magnesium (Lopez-Aliaga et al., 2003), zinc and selenium (Alferez et al., 2003). In addition, goat milk was found to be advantageous over bovine milk because it sustained high calcium availability without restriction of iron utilization, as it frequently the case with bovine milk (Nestares et al., 2008). The vast majority of these animal

studies indicate that goat milk is superior over bovine milk, in regard to fatty acid and mineral utilization.

In contrast to these studies with unformulated goat milk, mineral and amino acid digestibility of goat milk infant formula was similar to whey adapted cow milk infant formula (Rutherfurd et al., 2006a, b). In a randomized, double-blind comparison of growth in infants receiving goat milk infant formula versus cow milk infant formula, weight gain, head circumference and body length of infants fed goat milk formula was not significantly different from infants fed cow milk formula (Grant et al., 2005). These animal and human studies confirm the concept that infant formula made from goat milk is a suitable source of nutrients for infants and children. The lack of any differences in these studies between goat and cow milk formulas most likely reflects the fact that any commercial milk-based powdered food intended for infants, is strictly formulated for its vitamin and mineral content; thus, cancelling some of the natural advantages of goat milk over cow milk. However, the relatively lower allergenic burden of goat milk, easier digestion and the physiological benefits of goat milk described by Prosser et al. (2004) or Lara-Villoslada et al. (2006), suggest that formulas based on goat milk might prove to be advantageous in particular stressful situations, or for sectors of the population suffering from cow milk allergy, or pro-inflammatory intestinal diseases.

4. Food safety

When considering food safety, the major aspects usually thought of are: i) potential source of infection by zoonoses (defined as pathogens which may be transferred from an infected animal to humans and thereby causes a disease in the infected humans); ii) source of human specific pathogens, or pathogens that produce toxins, thereby, affecting all organisms, including humans; iii) presence of undesirable substances from the

animal's diet or inappropriate use of antibiotic, disinfecting and cleansing substances, etc. These are considered below.

4.1. Goat milk as a source of zoonoses

The risk of zoonoses has increased owing to globalization and geographical movement of humans, animals and goods. Diseases which were once confined to specific geographical areas are now capable of being rapidly spread by modern transportation systems. This situation results in new regulations, restrictions and implementation of control systems of animal and goods traded in different parts of the world (see Acha and Szyfres, 2003 for review). Goat milk products are consumed in many societies around the world as drinking milk, fermented milk products and cheese. Therefore, goat milk could serve as a potential vehicle for transferring of zoonoses, especially due to the fact that goats are a major property in countries where veterinary medicine is not optimal. The key technological barrier reducing the risk of spreading zoonoses in milk to consumers is the widely adopted heat treatment, either by boiling the milk or, in more sophisticated practices, by its pasteurization. The most common zoonoses known to be involved with goat milk are Brucellosis, Q-fever and toxoplasmosis, though some others are known. The etiology and symptoms of infection by zoonoses are well defined (Acha and Szyfres, 2003) and therefore will not be considered further in this review.

4.2. Goat milk as source of infectious pathogens and their toxins

Occasionally a lactating animal's udder becomes infected with hemolytic streptococci of human origin, which may result in milk-borne epidemics of scarlet fever or septic sore throat. The toxins of staphylococci and possibly other organisms in milk

may also cause severe gastroenteritis. Some of these toxins are not destroyed by pasteurization (Leedom, 2006; PMO, 2003). The most prevalent problem with goat milk-borne bacterial contamination is alimentary toxicosis and the most prevalent cause is the presence of *Staphylococcus aureus* and its enterotoxin in milk and milk products (e.g., Cremonesi et al., 2007). However, there are occasional reports or even outbreaks of alimentary toxicosis involving other pathogens, including *Escherichia Coli* (Espie et al., 2006)*,* including coliforms that produce the *Shiga Toxin* (Cortés et al., 2005; Muehlherr et al., 2003; Picozzi et al., 2005), *Salmonella enterica* serotype *paratyphi* B (Desenclos et al., 1996), and *Streptococcus equi* subspecies *zooepidemicus* (Francis et al., 1993; Kuusi et al., 2006). In addition, there are several reports on the presence of *Listeria monocytogenes* in raw milk (Leedom, 2006; Foschino et al., 2002; Soncini and Valnegri, 2005). This gram positive bacteria can infect infants born vaginally, causing meningitis; thus, pregnant mothers are often advised not to eat soft cheeses such as Brie, Camembert, feta and queso blanco fresco, which may be contaminated with and permit growth of *L. monocytogenes* (Genigeorgis et al., 1991). We would like to note, that these do not represent a systematic review of the literature on pathogens in goat milk and it is possible that more cases remained unnoticed, or unreported. It should also be noted that as a general rule, infections with pathogens from milk and dairy products usually only happens in cases where the victims drink unpasteurized milk, or eat fresh cheese made from unpasteurized milk (Leedom, 2006).

In Europe and the USA, the main regulatory mean to prevent the occurrence of zoonoses and other pathogenic bacteria and their toxins in marketed goat milk is through bacterial count of the raw milk (Pirisi et al., 2007). Bacterial count is defined as the number of aerobic colony-forming units (CFU) which develop when samples are incubated at a temperature of 30 ºC. In dairy cows it is also customary to count the CFU

of psychrotrophs (i.e., bacteria that multiple at temperatures < 10 ºC and therefore are resistant to cold storage) in the collected milk to provide information on the quality of milk storage in the farm tank.

Based on the potential pathogenic issues described previously there is a reason to implement more stringent food-safety control system in the dairy goat industry. Here, we will restrict our discussions to those aspects that may be applied on the farm. Adding the counts of psychrotrophs may be a valuable criterion not only for the evaluation of milk storage conditions, but for the likelihood of its contamination with pathogens. This is because in good quality milk the number of psychrootrophs would usually account for 90% or more of the total bacterial counts. Thus, in the situation of high bacteria count, any significant difference between total bacterial count and the number of psychrotrophs may suggest that the milk is infected with undesirable bacteria. Such a situation might necessitate imposition of a differential bacterial count to ensure that it does not contain infectious pathogens, before it could be used for human consumption. Another feasible means to improve milk hygiene is to include somatic cell count in milk grading in the form of a payment scheme, as is discussed further in the next section.

In any case, an effective program of prevention of the entry of zoonoses and pathogenic bacteria into products for human consumption can only be assured if it includes regular monitoring of the bacterial infection status of goat herds by the appropriate national veterinarian authorities and regular testing of products by the dairies prior to release to the market.

4.3. Milk hygiene: The need for standardization based on somatic cell count

Milk of various mammals, including goats, contains a heterogeneous population of cells, commonly referred to as somatic cells (SC). In most species, the predominant

cells in bacteria-free glands are leukocytes, composed of lymphocytes, polymorphonuclear neutrophils and macrophages, which serve as important components in defense of the mammary gland against potential pathogens, mostly bacteria. Milk also contains sloughed epithelial cells. The engulfment of sloughing apoptotic epithelial cells by macrophages and intact epithelial cells ensures their elimination without induction of inflammation. In dairy cows, a large proportion of the SC (40%) in uninfected udders is composed of epithelial cells (Leitner et al., 2000). One report indicates that 27% of SC in goat milk are epithelial cells (Boutinard et al, 2002).

In dairy cows, somatic cell count (SCC) is widely used for evaluating milk quality and to rank milk prices (PMO, 2003). This is because an elevated SCC is a consequence of an inflammatory process due to the presence of an intramammary infection (IMI) SCC of milk is considered a sensitive marker of udder health condition in goats as well (Raynal-Ljutovac et al., 2005, 2007). The basal level of SCC in bacteria-free udders of goats (~300,000 cells/mL), and sheep (~200,000 cells/mL) is fundamentally higher than in dairy cows (~70,000 cells/mL), hence, the level of SCC with udder infections is usually much higher in goats and sheep than in cows. This means, that a milk grading scheme based on SCC in goats and sheep should be specifically accommodated to the particular situation in these two species, and can not simply be adapted from those established in cows (Raynal-Ljutovac et al., 2007). Many non-infectious factors can also cause considerable variation in SCC in goat milk (Raynal-Ljutovac et al. 2007). One problem unique to goats is the marked elevation of SCC in milk coming from bacteria-free glands toward the end of lactation (Raynal-Ljutovac et al., 2007). Thus, a solution to this problem is necessary before applying quality schemes based on SCC for goat milk. One possibility that is being considered in Israel is to separate the milk collected from late lactating goats and allocate this milk for marketing solely for drinking, as this

late-lactation milk is less suitable for cheese making (Merin and Leitner, are board members in an *ad-hock* committee that should outline recommendations on this aspect to the Israeli Dairy Board).

The etiology of udder infections in goat flocks in Israel was recently found to be very similar to that in dairy cows (Leitner et al., 2007): i.e., it was composed of a high proportion of IMI acquired at the start of the dry period and at the beginning of lactation, whereas acquisition of new infections during lactation was very low. In addition, as in cows, a significant proportion of the yearling does join the herd already infected with mammary gland pathogens. The similarity to dairy cows, most likely relates to the similar intensive dairy husbandry systems.

Novobiocin-sensitive coagulase negative staphylococci (CNS) appear to be the most prevalent pathogen group, accounting for 58 and 93% of the bacteria that cause IMI in goats across various countries and geographical zones (Contreras et al., 2007; Haenlein, 2002; Raynal-Ljutovac et al., 2007); the situation with IMI in sheep is quite similar (Raynal-Ljutovac et al., 2007). Based on this relatively mono-prevalence of bacterial infections and on series of studies on both the herd and gland level infection within individual animals (Leitner et al., 2004a,b,c; 2006; Merin et al., 2004), Leitner et al. (2008a) proposed a scheme for grading milk of goats and sheep. With regard to goats, the recommendations were:

Grade A: SCC $\leq$ 840,000 cells/mL, associated with subclinical bacterial infection of up to 25% of goats in the herd, milk loss of up to 0.8% and curd loss of up to 3.3%.

Grade B: SCC > 840,000 and lower than 1,200,000 cells/mL, associated with subclinical bacterial infection of up to 50% of goats in the herd, milk loss of up to 1.5% and curd loss of up to 6.5%.

Grade C: SCC > 1,600,000 and lower than 3,500,000 cells/mL, associated with subclinical bacterial infection of up to 75% of the goats in the herd, milk loss of up to 2.3% and curd loss of up to 9.8%.

According to this proposition, milk with > 3,500,000 cells/mL should not be accept for marketing because i) The high probability that such milk will contain pathogens and toxins, ii) Its poor industrial quality (mostly poor or complete absence of curdling), and iii) The potential formation of toxic radicals substances in the milk (see Silanikove et al., 2005a, 2007; Merin et al., 2008 for the physiological and biochemical basis).

SCC is considered not only as an indicator of IMI, but also as a sensitive tool for analyzing the effects of IMI on milk yield, milk composition and efficiency of curd and cheese production, and other factors negatively influenced by IMI (Raynal-Ljutovac et al., 2007). Indeed, many reports confirm the significant negative interrelationship between SCC and these variables. However, in making these observations, we are measuring the interrelationship between two depended variables, and not between independent (i.e., a causal factor) and dependent (i.e., responsive factor). SC, though an important factor in response to IMI, is only one of the many responses to IMI (Leitner et al., 2006). Thus, this approach has its advantage as a working model as long as it yields valuable predictions, which is not always the case. In Israel, where bovine SCC in the farm bulk milk tank in most herds is reduced to ~200,000 cells/mL, which is only 3 times the level of that of uninfected cows, SCC loses its predictive value for curd yield, although the effect of subclinical IMI on milk quality still remains (Leitner et al., 2008c). Thus, as is the case for dairy cows, better predictors than SCC for grading of goat milk quality for manufacturing purposes will be needed.

Collectively, our studies on bovine milk suggest the following (Leitner et al., 2006; Leitner et al., 2008c; Silanikove et al., 2007): i) most of the reduction in milk yield from IMI (see for more details section 5) and deterioration of milk quality occurs during storage of the milk within the udder between successive milkings; ii) Irreversible damage to casein micelles that impede subsequent curd formation is a consequence of oxidative stress associated with the immune response to invading bacteria and elevation of plasmin (the main proteolytic enzyme in milk), and other proteolyitic enzymes; iii) The damage to milk quality is due to bacteria and is specie-specific. Infection with *E. coli* and *S. dysgalactiae* were found to be particularly devastating; iv) The most novel finding was that some casein-derived peptides impede curd formation (Merin et al., 2008). Thus, degradation of caseins represents not only a material lost for curdling, but also a source of factors that impede curdling.

In summary, under the current prevailing situation in most goat industries worldwide, applying SCC measurements as a routine management tool is highly recommended because it should help in defining milk quality, preventing food toxicity and searching for strategies to improve milk yield and quality. The scheme proposed in this review would provide the dairy with a tool to grade the milk it receives according to its hygienic quality, while providing the farmers with an insight of how much milk and curd they lose due to a given SCC or infection rate within the herd. Thus, verifying and applying this scheme or similar adaptive schemes as a working model in other countries might prove to be a valuable management tool.

4.4. *Contamination of milk with undesirable substances*

Contamination of milk with foreign substances that are used on the farm, such as antibiotics and cleansing or disinfecting substances is due to carelessness of the farmer.

Because of the prevalence of antibiotics in use by dairy farms, in many countries, the milk is routinely checked for antibiotic residues. However, a peculiar problem with goats is a high proportion of false-positive results when applying the Delvo test, commonly used for antiobiotic residue testing (Ham et al., 2008). From discussions with farmers, our impression is that this problem is particularly evident in milk of goats on pasture, perhaps relating to the accumulation in milk of phytochemicals with antibiotic-like activity. Therefore, developing an appropriate analytical technique for the determination of antibiotic residues suitable for goat milk is of high importance.

The other major source of potential contamination of milk with undesirable substances is via animal feeds. The most prevalent contaminants in feedstuffs for ruminants, and which are a source of risk to public health, are mycotoxins, heavy metals, dioxins and similar pollutants. Contamination of agricultural products with heavy metals and toxic substances is a combination of problems associated with intensification of modern agricultural practices, increased industrial pollutants in the environment and use of sewage sludge in agriculture (Kan and Meier, 2007; Pulina et al., 2006). Heavy metals, such as Zn, Cu, Cr, Ar, Pb and Cd, and toxins such as dioxin and perchlorates have potential to accumulate in dairy production systems. These topics are not peculiar to the dairy goat industry, and the risk of contamination of dairy products and other food sources is the responsibility of the respective appropriate health authorities for every country. The scientific context of considering the physiological basis for the accumulation of environmental contaminants in milk was recently reviewed (Pulina et al., 2006). As the general considerations are the same for all ruminants, and since there is no specific information in this respect for goats, this topic will not be considered further in this review.

Mycotoxins are secondary metabolites produced by some species of moulds that grow on food. Mycotoxins may produce a range of ill effects such as nephrotoxic, carcinogenic, teratogenic, immunotoxic, and hepatotoxic if consumed by humans (IARC, 2002). Contamination of feedstuffs may occur at any stages of their production cycle (i.e., cropping, harvesting, transport, storage). Although some mycotoxins seem not to be toxic to goats and sheep, some of their metabolites may be transferred to milk, thus creating a potential risk to dairy consumers. Two major types of mycotoxins, i.e., ochratoxins and aflatoxins are widespread. Ochratoxins are degraded quite effectively by rumen microorganisims, and there are only two reports on their occurrence in cow milk in Norway and Sweden (Pulina et al., 2006). To the best of our knowledge, nothing was reported on the occurrence of ochratoxins in the milk of goats.

Aflatoxins are fungal toxins that are produced mainly by *Aspergillus flavus* and *A. parasiticus*, which occur in several important feedstuffs, such as peanuts, maize grains and cottonseed. Aflatoxin B1 (AFB1) is the most toxic compound produced by these moulds. Aflatoxin M1 (AFM1) is the hydroxylated metabolite of AFB1 and may enter milk and milk products of animals that have ingested feeds contaminated by AFB1. Consumption of milk and milk products is one of the principal ways in which aflatoxins are introduced into human diets (Galvano et al., 1998). The International Agency for Research on Cancer of WHO (IARC, 2002) includes aflatoxins among the substances which are carcinogenic to humans (Group 1). Several countries have regulated the maximum permissible levels of AFB1 in food and AFM1 in milk and dairy products. The European Union established 50 ng/kg as the maximum allowed concentration of AFM1 in liquid milk (Pulina et al., 2006). In contrast, the USA-FDA as well as the FAO/WHO Joint Expert Committee on Food Additives established a maximum AFM1 concentration level of 500 ng/kg in milk (Pulina et al., 2006). Because of the tendency

of AFM1 to bind to the protein fraction of milk, the toxin can contaminate dairy products. Cheese curd made from contaminated sheep milk had an AFM1 concentration about two-fold higher than that of the respective milk, through the concentration of casein within the product (Battacone et al., 2005). In a recent study from Italy (Virdisa et al., 2008), AFM1was detected in ~10% of samples of ripened goat cheese at levels of between 79.5 ng/kg and 389 ng/kg; all of the contaminated samples were obtained from the same cheese manufacturer. In another study from the City of Kilis in Turkey (Ozdemir, 2007), AFM1 was detected in ~85% of the samples, of which 6% were contaminated by AFM1 at hazardous levels for human health. Updated information on the presence of AFM1 in goat milk in various countries and geographical zones is meager. Nevertheless, based on the above, and similar findings in sheep (Pulina et al., 2006, for review), there is reason to suggest that the level of AFM1 in milk should be routinely monitored, to prevent the occurrence of hazardous levels of this toxin in goat milk or goat milk products in the market.

5. Milk production: Basic and applied management aspects

5.1. Introduction notes and historical perspective

Milk production is an outcome of a complicated balance between regulation of milk synthesis and its secretion into the gland lumen. Milk synthesis depends on proper gland development, nutrition, extraction of metabolite precursors from the blood and their conversion to exclusive milk products within the alveolar epithelial cells of the mammary gland. These in turn depend on complex endocrinological and physiological regulatory systems. It would be over-ambitious to cover all of these aspects in a single review, but attention is drawn to the part that goats played as a major experimental animal model in developing fundamental and classical concepts in this field of research.

Beginning in the 1930s, S.J. Folley and later on A.T. Cowie and I. Forsyth at the Institute for Research in Dairying at Reading (IRDR), England, defined the basic terminology to describe the phases of lactation (lactation stage I, lactation stage II), the hormonal requirements for mammary growth and lactation in the animal, the role of oxytocin in milk ejection and delineated the variety of precursors used by the mammary gland for lipid synthesis (e.g., Popjak et al., 1952). A second center of lactation studies was the Agricultural Research Institute at Babraham, England in the 1950s, by J. Linzell, and later on in Scotland with M. Peaker, at the Hannah Research Institute (HRI). These researchers contributed to the basic understanding of lactational physiology, including the development of the arteriovenous differences across the mammary gland of the lactating goat. This experimental technique eventually led to almost complete defining of nutrient uptake and utilization for synthesis of milk lipids, lactose and protein in goats, and culminated in an authoritative review on the mechanisms of milk secretion (Linzell and Peaker, 1971). Both IRDR and HRI are now closed; reflecting a worldwide shift of interest towards human related studies, particularly breast cancer as the main line of mammary-related research. However, some excellent modern studies of farm animals continue in other centers, and some of them are reviewed here.

In this review we would like to concentrate on the regulation of milk secretion, for two reasons: first, research with goats contributed to our basic understanding in this aspect, and secondly, the knowledge gained has application on our ability to contribute concepts and technologies for improving goat farming management.

5.1.1. Basic features in the regulation of milk secretion

The idea that milk secretion in goats, and thus the actual amount of milk released from the gland, is regulated by a milk-borne negative feed-back (MBNF) mechanism can be tracked back to quite an early stage in Linzell's and Peaker's careers (Linzell and Peaker, 1971). This idea has since become widely accepted and pertinent to all mammals, because of the unambiguous supporting evidence from studies with humans and mice, in addition to the earlier and more recent studies with goats and cows (see Silanikove et al., 2006 for review). Collectively, these studies have shown that changes in the frequency of mammary gland evacuation (within 24 to 48 h) acutely regulate milk secretion, and that the effect is specific to the manipulated gland (if the changes induce only in a specific gland). Generally, increasing milking frequency increases milk secretion rate, whereas extending the duration of milk stasis depresses it. There are wide interspecies variations in the responsiveness to the rate of gland emptying. The most sensitive species appears to be the lactating human female, with changes in rates of milk secretion becoming apparent between two breastfeeding events; i.e., within 2 to 3 hours. Among the domestic ruminants, goats appear to be the most tolerant towards increasing the time interval between milking episodes and the physiological basis for this are discussed below.

5.1.1.1. Milk-borne negative feed-back: current concepts

a) The FIL concept

Despite the fact that the MBNF regulatory concept was presented some 4 decades ago, the physiological concept underlying it is unresolved. Wilde et al. (1995), presented evidence suggesting that the local regulation of milk secretion by milk removal is through an autocrine feedback inhibition by a single whey protein from goat milk of Mr 7600, which they termed FIL (Feedback Inhibitor of Lactation). However,

despite the fact that more than a decade had passed since this work was first published, there is no information regarding the complete amino acid sequence of FIL or identification of the gene coding it. Furthermore, research on FIL appeared to have dwindled, and never independently supported by a non-HRI laboratory.

b) The plasmin-derived regulatory peptide affecting the potassium channel concept

In contrast to the FIL concept, the plasmin-based concept described below has been independently supported by two independent laboratories (Marnet and Komara, 2008; Pulina et al., 2005). Milk volume is determined by osmotic-coupled water flow; in goats and cows, with the secretion of K^+, Na^+ and Cl^-, providing approximately 40% of the driving force with the rest being determined by lactose (Shennan and Peaker, 2000). The currently held view is that lactose and monovalent ions are secreted into the lumen of the mammary gland mainly via Golgi-derived secretary vesicles (Shennan and Peaker, 2000). However, a direct contact between monovalent ions inside the epithelial cells and fluid stored in the lumen of the gland is possible, since the apical membrane of the epithelial cells contain K^+, Na^+ and Cl^- channels (Shennan and Peaker, 2000). This perspective led Silanikove et al. (2000) to test the possibility that ion channels expressed in the apical regions of mammary gland epithelium are involved in the regulation of milk secretion.

The involvement of the plasminogen activator (PA)–plasminogen–plasmin system in the control of gradual involution (the decline phase of lactation) was also known for quite a long time (Silanikove et al., 2006, for review). Plasmin preferentially cleaves polypeptide chains after a lysine or, to a lesser extent, an arginine residue. β-CN is the preferred substrate for plasmin and its hydrolysis results in the production of γ-caseins and β-CN f (1–28). Silanikove et al. (2000) showed that a distinct plasmin-induced β-

CN peptide f (1–28) is a potent blocker of K^+ channels in the apical membrane of mammary epithelial cells. No genetic substitutions in this part of β-CN have been found in goats and cows, so that all genetic variants of β-CN will result in the same fragment. These characteristics make β-CN f (1–28) an ideal candidate for negative feedback control of milk secretion in both species. Infusion of a solution composed of a casein digest enriched with β-CN f (1–28) into the cistern of cows, or infusion of pure β-CN f (1–28) into the cistern of goats, led to a transient reduction in milk secretion in the treated gland (Silanikove et al., 2000).

Stress and stress-related hormones such as glucocorticoids also inhibit lactation in cows (Shamay et al., 2002). Silanikove et al. (2000) proposed a novel mechanism connecting stress with the PA–plasminogen–plasmin system. They showed that stress activated the PA–plasminogen–plasmin system leading to an increased plasmin activity and formation of β-CN f (1–28). The reduction in milk production due to dehydration stress or glucocorticoid (dexamethsone) was correlated with the activity of plasmin and ion channel-blocking activity in the milk of the tested cows (Silanikove et al., 2000). Thus, the concept reviewed by Silanikove et al. (2006) provides an explanation for the already-known correlation between the activity of the above systems and reduced milk secretion. Accordingly, activation of the hypothalamus–pituitary–adrenocortical axis by external stress liberates cortisol into the blood plasma, which in turn induces the liberation of PA from the mammary epithelial cells into the mammary cistern, where it activates the plasmin system and enhances the release of β-CN f (1–28) from β-CN. Inhibition of ion channels by β-CN f (1–28) triggers an as yet unknown process, which reduces the secretion of lactose and monovalent ions into the lumen of the gland, leading to the decrease in milk volume. This rapid modulation of milk secretion increases the potential for survival in response to stress.

Milk stasis also induces the disruption of tight junctions between epithelial cells due to the accumulation of local negative feedback signals (Silanikove et al., 2006). It was shown in goats and cows that treating mammary glands with casein hydrolyzate (CNH) caused a disruption of the tight junctions within 8 h after the first treatment followed by complete involution of the treated glands. Thus, these data suggest that the first step in the induction of involution in the mammary gland is disruption of the tight junctions between epithelial cells. Keeping tight junctions open for a critical time (about 48 h) initiates the second phase of involution, which is irreversible. Silanikove et al. (2006) review provides strong evidence that the mammary gland may undergo partial involution while the animal is still in the lactogenesis phase.

Intrammamary treatment with casein hydrolyzate (CNH) was shown to be an effective non-antibiotic treatment to cure sub-clinical and clinical infections (Silanikove et al., 2005b) and during the dry period in cows (Leitner et al., 2008b), by the abrupt reduction in mammary secretion and stimulation of the gland's immune response (Silanikove et al, 2005a). As CNH treatment proved to be effective in goats as well (Shamay et al., 2003), there is scope for CNH intrammamary treatment as an effective dry period and therapeutic treatment for mastitis in goats.

c) Milking frequencies in respect to the plasmin-related MBNF regulatory concept

In a recent review we have discussed the ability of the plasmin-related MBNF regulatory concept to explain the response of dairy cows to an increase, or a decrease in milking frequency (Silanikove et al., 2006).

Once-daily milking is more of a traditional milking routine for goats in Europe [Canaries breed (Capote et al., 2008); Murciano-Granadina breed (Salama et al., 2003, 2004) and in Asia Minor, Damascus breed (Papachristoforou et al., 1982)], than sheep

and cows. The use of this system in goat farms reflect the fact that many of the farmers devote a large proportion of their activities to producing and selling dairy products (mainly cheese), as an important part of their income. Typically, the drop in milk yield is moderate and partially compensated by an increase in milk protein and fat concentrations in low- to average-milk producing goats on a once-daily milking regimen. Once a day milking of Murciano-Granadina dairy goats moderately reduced milk yield without negative effects on milk composition and udder health (Salama et al., 2003, 2004). These losses were lower during mid- or late-lactation and in older goats.

In high-yielding goats (frequently over 1,000 L per lactation) losses are significant (Marnet and Komara, 2008). In goats in which the response is small to moderate (-15%) no leakage of milk, no specific vocalization or increase in restlessness at the time when milking was suppressed were observed, suggesting minimal adverse effects on production or animal welfare (Marnet and Komara, 2008). However, in Alpine goats with a moderate reduction in milk yield under once-daily milking regimen, there was considerable variability among animals, with some goats having milk production reduced by nearly 30%, similar to Holstein cows milked once-daily, whereas in other goats milk yield was decreased by no more than 2%. Alpine goats, unlike Saanen, are frequently used in grazing systems in Provance, France. Thus, divergent selection for high and low milking frequencies may account for high variability in this breed.

Typically in goats, 24-h of milk stasis is necessary to activate regulatory mechanisms leading to disruption of tight junctions and reduced milk secretion, longer than the 18 h required to induce a similar phenomena in cows and sheep (Marnet and Komara, 2008). Studies with cows indicate that a large storage capacity within the gland cisterns allows undisturbed flow of milk from the alveolar compartment to the cistern, providing the animal with a greater capacity to counteract the negative effects of the

accumulation of milk. (Marnet and Komara, 2008, for review). Goats have a higher proportion of milk in their cistern than ewes or cows (70 to 90% of the total udder volume), which most likely contributes to their ability to better maintain milk yield under once-daily milking. For example, in goats, cisternal to alveolar ratio increased with milking interval (Capote et al., 2006). Despite extended milking intervals, cisterns of goats milked once a day did not become larger than cisterns of goats milked twice a day after 5 wk of treatment. Within goats, multiparous goats had larger cisterns than primiparous goats and were able to store more milk in their cisterns at all milking intervals. Because of the high capacity of goat cisterns, no milk return from the cistern to the alveoli is expected if milking is delayed after milk letdown. Similarly, it was demonstrated recently in sheep that the degree of leakiness of epithelial tight junctions differed according to breed, being more pronounced in Manchega (small udder cisterns) than in Lacaune ewes (large udder cisterns) (Marnet and Komara, 2008).

In conclusion, the small difference between once-daily and twice-daily milking regimens which were found in low to moderate producing goats relates to a high udder volume of the goat (López et al., 1999), in particular with large cisternal capacity that allows a continuous drop of alveolar milk and therefore delays the effect of the intramammary feedback inhibition. This between- and within-species variability in response to milking frequency may be explained in light of the plasmin-related MBNF regulatory concept. Accordingly, the cistern should be regarded as a separate compartment from the alveolus. This separation is a consequence of lack of fluid reflux from the cistern to the alveoli (Capote et al., 2008; Salama et al., 2003, 2004), and attenuated back (up-stream) diffusion of soluble components as long as there is a positive gradient in pressure from the alveoli to the cistern. It is predicted that for milking intervals of less than 20 h in goats and 18 h in cows, the concentration of

casein-derived peptides, including the active component β-CN f (1–28), would be higher in the cistern than in the alveoli; therefore, the alveoli will not be exposed to the full impact of the negative feed-back signal of this peptide. Extending milk stasis beyond these times exceeds the storage capacity of the cistern, resulting in the equilibration of β-CN f (1–28) concentration between the cistern and the alveoli. Exposing the alveoli to high concentration of β-CN f (1–28) will induce disruption of the tight junction and thus, involution stage I (the reversal stage of involution). Since the equilibration between cistern and alveolar β-CN f (1–28) concentration is predicted to be gradual, the negative effect on milk secretion into the alveoli is expected to precede the opening of the tight junction.

According to this model, high producing goats should be selected for udder conformation and ease of milking; these animals will tend to have relatively high proportion of the cistern and will be the most sensitive to changes in milking frequency. A classical breed for demonstrating such a selection-trend would be the Saanen. Medium to low producing goats may attain their genetic potential for milk yield in a once a day milking regimen due to selection for high cistern capacity. Appropriate breeds for such selection are those adapted, both for confinement and range conditions, such as the Alpine, Anglo-Nubian and Damascus (Shami) breeds. These breeds are expected to have high variability in their cistern capacity, a proposition that was already shown in the case of Alpine goats (Marnet and Komara, 2008). Some breeds such as the Tinerfeña and Murciano-Granadina dairy goats are already selected toward such a trend.

d) The negative effects of subclinical mastitis relative to the plasmin-related MBNF regulatory concept

Recently our group have compared the effect of subclinical infection in one gland in comparison to an uninfected gland in the same animal on milk composition and yield in sheep (Leitner et al., 2004a), goats (Leitner et al., 2004b,c) and cows (Leitner et al., 2006). Milk yield was reduced in the infected glands in comparison with the uninfected ones and these changes were associated with increased plasmin activity, indices of inflammation (SCC, NAGase activity), proteolysis of casein (increased proteose–peptone content and lower casein number) and a decrease in lactose concentration. However, the results for fat, total protein and casein concentration were variable. In the case of sheep, a significant decrease in fat, total protein and casein concentration and a significant increase in whey protein concentration were observed. In the case of goats, subclinical mastitis was associated with no change in fat concentration and a significant increase in total protein, but with no change in casein level and with a significant increase in whey protein concentration. In the case of cows, infection was not associated with changes in fat, total protein or casein, but was associated with increase of total whey protein concentration. In view of the evidence for extensive degradation of casein in the infected glands, the lack of response in total casein concentration in goats and cows is striking. This contradiction may be explained as an outcome of the reduction in casein secretion and casein content due to enhanced hydrolysis and the increased casein concentration as a result of a greater reduction in fluid secretion. The more severe response in sheep, in comparison to goats and cows, is consistent with a higher basal level of plasmin activity, a higher level of plasmin activity in the infected glands, a higher basal level of casein, and hence a higher level of casein degradation products (i.e., proteose–peptone) in the infected glands. These inter-species differences are also associated with a greater reduction in lactose concentration in sheep than in goats and cows, in line with the primary osmotic pressure role of lactose in milk and its effect on

fluid secretion (Shamay et al., 2000). In comparison to sheep and cows, goats have lower level of plasminogen (Fantuz et al., 2001; Silanikove et al., 2000). As inferred by the scheme depicted in Fig. 1 in Silanikove et al. (2006) goats would be less affected than cows and sheep by environmental stresses which activate the MBNF, owing to the lack of plasminogen for response. Indeed, Shamay et al. (2000) have shown that goats resist much higher doses of dexamethasone (a potent analog of the stress hormone, cortisol) than those used to depress milk secretion in dairy cows.

In summary, goats appear to be the least affected ruminant species in respect to physiological manipulations (lower milking frequency), IMI and environmental or emotional stresses that reduce milk secretion. These advantages are explained by their unique morphophological and physiological features and the above-described plasmin-related MBNF.

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