We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Role of Goat Milk in Infant Health and Nutrition

Marzia Albenzio, Francesca d'Angelo and Antonella Santillo

Abstract

Goat husbandry is widespread due to high adaptability of goat to different and extreme environments. Goat milk is valuable from a nutritional point of view in terms of both protein and lipid fraction. The complex polymorphism of its casein fractions as well as the peculiar fatty acid profile makes goat milk interesting for its high potential in exploitation for human health. Genetic polymorphisms of milk proteins play an important role both in eliciting different allergic reaction and for derived peptides with functional properties. The purpose of the present chapter is to report information on the possible impact of goat milk protein and lipid fractions on cow's milk protein allergy, and on some infant diseases as generalized epilepsy and metabolic disorders.

Keywords: caprine casein polymorphism, caprine fatty acid profile, cow milk allergy, infant epilepsy, infant obesity

1. Introduction

The most represented animal species in terms of milk productions are cow (81.05%), buffalo (15.14%), goat (2.25%), sheep (1.20%), and camel (0.35%) that contribute differently to milk world production [1].

Milk represents the first food for each newborn, able to satisfy the nutritional needs differently based on yield and composition. Although the proximate composition of goat milk is quite similar to cow milk, the former has received increasing attention due to its peculiar protein, fat and mineral composition and bioactive components.

Greater digestibility has been attributed to goat milk due to its casein curd, which is softer and smaller and makes it more easily attached by human digestive system than that derived from other milks. Moreover, size of the fat globules and high proportion of short and medium chain fatty acids also affect the digestibility since it provides a better dispersion and a more homogenous mixture of fat.

Although the content of lactose in goat milk is comparable to that of other milk-ing species, goat milk is rich in lactose-derived oligosaccharides (OS), especially fucosylated and sialylated OS, which are not degraded by human digestive enzymes and exert prebiotic and antimicrobial functions in the gastrointestinal tract.

An appropriate nutritional intake in childhood is required for not only growth and development but also to support health and immune functions, with short and long-term implications for human well-being. Goat milk has always enjoyed particular attention for its beneficial effects in human nutrition, in particular for fragile categories such as infants and the elderly, even if the potential benefits attributed to such milk were based more on anecdotes than on scientific data.

To date, scientific evidence collected in more than 70 years of scientific research and corroborated by recent advances in milk biochemistry and *in vivo* and *in vitro* studies aimed at evaluating the effects of milk components on human physiology, bring great attention to goat's milk for its nutritional and medical value.

2. Methods

The present chapter reports recent advances on the role of goat milk in several aspects of infant health. In particular, the peculiar composition of goat milk protein and lipid fractions has been deepened with the aim to exploit the use of such milk in infant nutrition.

The complex genetic polymorphism of casein fraction of goat milk may offer a strategy in the treatment of cow milk allergy, due to the low amount of casein fractions in milk proteome. The study of the inflammatory response to goat milk in terms of cytokines production by peripheral blood mononuclear cells (PBMCs) stimulated with milk protein fractions represents a novel approach aiming at verifying the effective role of goat milk in the treatment of infants with cow milk allergy. PBMCs are easily isolated from blood and are used to investigate the effect of food bioactive molecules on various immune cells.

The impact of milk protein mixture, casein and β -lactoglobulin fraction on cytokine production by PBMCs from infants with cow's milk protein allergy is discussed in the present chapter. Ten patients with cow's milk protein allergy and ten non-allergic control infants were included in the study [2].

The composition of protein fraction has been investigated for its role in infant epilepsy by means of *in vitro* system using PBMCs collected from 10 children with generalized epilepsy and 10 control children [3]. The level of cytokines, produced in response to purified casein and whey protein fractions, obtained from goat milk and milk from human and other milking species, represents a tool to evaluate the pro or anti-inflammatory role of food in triggering the epileptic seizures.

Cytokines secreted by PBMCs are soluble polypeptides and glycoproteins that bind to specific receptors and are extremely potent at low concentrations. Their potency is partly due to the regulation of leukocyte function during inflammation.

The effect of protein fractions from milk on the production of cytokines and reactive oxygen species (ROS) of PMBCs from infants with generalized epilepsy was studied.

Levels of TNF- α , Interleukin-10 (IL-10), IL-6 and IL-1 β in culture supernatants were determined using Luminex Multiplex Assays, while the level of ROS was measured in the culture supernatants using an OxiSelect *in vitro* ROS/RNS assay kit.

The effect of the four casein fractions and the mixture of the two main whey milk proteins from different ruminant species (cow, sheep and goat) on cytokines and oxidative phenomena in PBMCs from children with generalized epilepsy are discussed in the present chapter [4]. Separation of milk protein fractions was obtained using reversed-phase (RP)-HPLC.

PBMCs were obtained by density gradient from blood of 10 children with generalized epilepsy and 10 controls. Children with epilepsy were grouped according to cytokine levels as follows: one group having levels of cytokines comparable to those of the control group; a group with cytokine levels at least 5-fold higher than the control group; and a last group having cytokine levels at least 10-fold higher than those of the control subjects. The production of TNF- α , IL-10, IL-6 and IL-1 β was studied in PBMC cultures, incubated with the four different casein fractions and a mixture of α -Lactalbumin and β -Lactoglobulin from dairy cows, sheeps and goats. In the cultured supernatant were also measured the levels of reactive oxygen species (ROS).

Finally, the present chapter gathers information on the peculiar fatty acid profile of goat milk lipid fraction and on the factors influencing the increase of fatty acids with beneficial role in human health. With this regard, the acidic profile of milk and digested milk has been studied with the aim to sustain infant nutrition in the prevention of metabolic disorders as childhood obesity.

The effect of *in vitro* digested milk on mature adipocytes 3 T3-L1 was studied comparing milk from different species including human [5]. Cellular viability, apoptosis, oxidative response and gene expression levels of NF- κ B p65 and HMGB1, involved in the regulation of inflammatory response, were evaluated.

In order to mimic milk digestion, simulated salivary fluid at pH 7, gastric fluid at pH 3, and intestinal fluid at pH 7 were prepared. Adipocytes *in vitro* model has shown the potential to study the role of goat milk in relation to preadipocyte differentiation, mediated immune response and oxidative status.

3. Protein fraction in caprine milk

In-depth studies have revealed that goat milk is characterized by the presence of numerous polymorphisms in the loci of casein. The different alleles, depending on whether they are strong, weak or null, are associated with different levels of casein synthesis in milk and with different phosphorylation and glycosylation rates of the peptide chain.

According to the technological properties of milk, goat's milk from subjects with strong alleles was associated with a greater activity of milk coagulation enzymes, resulting in a greater inclusion of nutrients in the curd, higher yields in cheese and more compact curds with respect to the milk of animals carrying weak alleles. In fact, it has been shown that homozygous goats for strong alleles (in particular CSN1S1 AA goats) are able to more effectively use food proteins and high-energy diets, resulting in the production of milk that is richer in proteins and fats [6]. The milk of animals with strong genotype also has larger fat globules and a better creaming ability than the milk of goats with null genotype [7]. Furthermore, the CSN1S1 genotype influences the concentration of some fatty acids (FA): goat's milk homozygous for strong alleles have a higher content in short and medium chain FA (SCFA and MCFA), mainly synthesized *de novo* in the mammary gland, less branched chain (BCFA) mainly derived from rumen bacteria and less odd chain FA (OCFA) partly derived from rumen bacteria and partly from *de novo* mammary synthesis from C3 precursors. Indeed, CSN1S1 defective alleles induce negative feedback on *de novo* fatty acid synthesis in goat mammary epithelial cells.

3.1 Role of caprine milk in treatment of cow milk allergy

Goat milk offers advantages in treating people afflicted with cow milk allergies (CMA) and gastro-intestinal disorders [8]. Cow's milk allergy is the most commonly reported childhood food allergy; recently a pan-European birth cohort study using the gold standard diagnostic procedure for food allergies confirmed challenge-proven CMA in <1% of children up to age 2 [9]. It has been reported that children affected by gastrointestinal allergy and chronic enteropathy against cow milk could be beneficially treated through goat milk therapy; although some caprine milk proteins could exert immunological cross reactivity with cow milk proteins [10]. Children with CMA present a high risk of reaching out to side reactions to other mammalian milks, so goat's or ewe's milk-based formulas or products may be used only after individual testing. High casein polymorphism and check for the absence of cross-reactivity could lead in future to a therapeutic approach based on personalized nutrition.

In pediatric patients with CMA, IgE-binding epitopes on α s1-casein, α s2-casein, β -casein, κ -casein, β -lactoglobulin, BSA, IgG heavy chain, lactoferrin were recognized [11].

A novel approach has been conducted to study the inflammatory response to goat milk in infant with CMA by evaluating cytokines production by peripheral blood mononuclear cells (PBMCs) stimulated with whole milk, casein and β -lactoglobulin [2]. Goat milk proteins lowered the production of pro-inflammatory cytokines and enhanced the release of anti-inflammatory ones from PBMC compared to cow milk. In particular, secretion of the regulatory cytokine IL-10 after PBMC stimulation suggests that goat milk might prevent aberrant reactions towards antigens. Indeed Tiemessen [12] studied the role of IL-10 in T-cells reactivity of children affected by CMA highlighting the possibility that activated allergen-specific T-cells might concur to the formation of an active form of immune suppression *in vivo* through the production of IL-10. At the same time, TNF- α displayed lower level after stimulation with casein fractions isolated from goat than from cow milk in children with CMA. However, it is important to test the immune reactivity against each protein fraction before considering goat's milk as a safe substitute for feeding infant with CMA.

The level of synthesis of each protein fraction in milk due to genetic polymorphisms plays an important role in eliciting different degrees of allergic reaction. High frequency of the weak allele F, the presence of null allele for CSN1S1, and the high frequency of A0 genotype at CSN1S2 locus in goat breeds as Garganica goat makes this milk useful for testing on allergic subjects. Low levels of α s1-CN in goat milk means that its casein profile is closer to human milk than that of cow milk as human milk does not contain the α s1 -fraction and α s2 -fraction [13], while the major constituent is β -casein [14]. The phosphorylated serine residues of α S1 -casein, β -casein, and α S2 -casein appear to be an important allergenic epitope able to bind IgE even after a denaturing process. The α S1 -casein is characterized by linear epitopes released after protein digestion that can pass through the gastrointestinal system in immunologically active forms. The epitopes are mostly based in the primary sequence rather than in conformation. This is the reason why although extensively hydrolyzed formulas are considered the first choice for CMA treatment, these formulas have can also provoke an allergic reaction in some more allergic individuals, due to their residual allergenic epitopes [15].

Genetic polymorphism of goat milk proteins involved in human health and nutrition, associated with a different composition of milk proteins, may be responsible for the generation of a broad spectrum of casein-derived peptides [16]. Therefore, the study of the potential bioactivity of the peptide sequences released after hydrolysis plays a role of considerable relevance.

The study of goat casein loci can lead to a differentiation of the goat population, based on the final use of milk. Animals characterized by weak or null casein alleles could be used in breeding programs aimed at producing milk with hypoallergenic properties, while animals with strong alleles could be destined to improve the quality and properties of milk and related products [3].

In ruminant species, proteolytic activity in fresh raw milk can be attributed to indigenous enzymes, which originated from the animal, and to microbial (i.e. endogenous) enzymes. The major proteolytic system in milk is ascribed to the plasmin system, an alkaline serum proteinase system, and to cathepsins and elastase. Santillo et al. [17] investigated the effects of indigenous proteolytic enzymes on the release of bioactive peptides from goat milk. The authors have identified serine proteinases, and in particular plasmin, as protagonists in the release of numerous peptides deriving from β -CN and α s2-CN which could be considered bioactive molecules. The majority of the peptides showed similarity in the structure with

bioactive peptides elsewhere described in goat and bovine milk and in dairy products. Some of the peptides have been shown to perform ACE inhibitory activity or have shown similarity in the structure with antihypertensive or antioxidant peptides.

3.2 Role of caprine milk in infant epilepsy

Epilepsy includes a group of neurological disorders characterized by periodic episodes of spontaneous seizures; the World Health Organization estimates this disorder affects 0.8% of the world population [18].

Several reports hypothesize the existence of a correlation between seizures and certain foods. The role of food products of animal origin on the diet has been widely recognized, especially with regard to the effects of protein fractions. In fact, milk proteins play an important role in stimulating the innate immune response, through the activation of pro and anti-inflammatory cytokines [2]. From this perspective, the effect of goat's milk protein fractions on the production of pro and anti-inflammatory cytokines was tested in newborn patients with epilepsy.

Cytokines are generally synthesized and secreted in response to immunological stimuli; they are soluble glycoproteins involved in growth regulation mechanisms, in the activation of immune cells and in inflammatory and immune responses, able to reach distant cells in other organs, through the peripheral circulation [19].

Stimulation with milk protein fractions from different milking species influenced pro and anti-inflammatory cytokines, produced *ex vivo* by PBMCs isolated from children with generalized epilepsy. Tumor necrosis factor- α produced by PBMCs cultured with caprine milk induced higher levels of this cytokine in 80% of infants. However, the levels of TNF- α detected in PBMC stimulated with goat's milk reached lower levels with respect to bovine and ovine milk. Regarding the TNF- α production, casein fraction induced lower levels in a higher percentage of patients, while the whey protein fraction induced higher levels of TNF- α in 10% of children, regardless of species. Furthermore, TNF- α produced by PBMC cultured with bovine and ovine whey protein was found to be lower in 70% of patients, while TNF- α produced by PBMC cultured with goat whey protein fraction showed intermediate levels in 80% of cases.

Bovine, caprine and ovine milk resulted in low IL-10 production by cultured PBMCs in at least 50% of cases, both for casein and whey protein fractions for all milk species studied. In general, the total amount of IL-10 detected was lower than that of other cytokines involved in this study. Interleukin-10 exerts extensive anti-inflammatory properties thanks to its inhibition of antigen-presenting cellular function and suppression of proinflammatory cytokines production [20]. Albenzio et al. [2] found higher levels of IL-10 in PBMCs cultured against cow and goat milk fractions in both healthy infants and infants affected by CMA.

Goat milk and casein fraction induced the highest levels of the same cytokine IL-1 β in 80% of cases and whey protein induced an intermediate level in 80% of cases. Interleukin-1 β is involved in promoting arousal toxicity and possibly in seizure generation [21]. There is a striking example of a dual role of cytokines on neuronal survival in diseased tissue; in particular, neuroprotective actions of IL-1 β have been reported, probably mediated by its ability to induce the synthesis of astrocyte growth factors, promoting cellular repair mechanisms. The chronic expression of IL-1 β during epileptogenesis suggests its involvement in the modulation of spontaneous seizures [22].

Caprine milk showed the highest level of IL-6 in 80% of patients, while bovine milk intermediate levels in 50% of patients, and ovine milk the lowest level in 60% of patients. The bovine and caprine casein fractions stimulated higher levels of

IL-6 in 80% of cases, while sheep casein stimulated a lower level in 80% of cases. In addition to the animal species, the whey protein fraction stimulated a lower level of IL-6 in most of the patients studied. The complexity of the PBMC response against stimulation by milk protein fractions can find an answer in the bivalent nature of IL-6, which is necessary for normal nervous system development but has neurotoxic and proconvulsive effects when increased levels are detected in the brain [23].

Subsequently the effect of milk protein fractions (α S1-CN, α S2-CN, κ -CN, β -CN, and a mix of α -LA and β -LG) from different animal species (bovine, ovine, and caprine) was evaluated on pro- and anti-inflammatory cytokines on infant patients [4]. Evaluating the production of cytokines by PBMC after exposure with milk protein fraction is of great interest to identify potential antigens in milk. In this study the patients were grouped as: 1) children with epilepsy having low levels of cytokines not different from those of control children (LL-EC); 2) children with epilepsy having cytokine levels at least 5-fold higher (medium levels; ML-EC) than those of control children; 3) children with epilepsy having cytokine levels at least 10-fold higher (high levels; HL-EC) than those of control children.

Table 1 reports the mean levels of TNF- α , IL-10, IL-6, and IL-1 β in PBMC from blood of children from HL-EC group, incubated with 100 μ g/mL of κ -CN, α S1-CN, α S2-CN, β -CN, and a mix of α -LA and β -LG obtained from bovine, caprine, and ovine milks. The results of this work demonstrate how complex interleukin modulation is in response to the different protein fractions, whether casein or whey protein.

Lower concentration of TNF- α was associated to PBMC incubated with bovine milk than with ovine or caprine milk. The major contribution to the elevation of TNF- α level was attributed to the β -casein fraction.

IL-1 β and IL-6 recorded lower level after incubation with caprine and ovine milk than bovine milk. The differences in cytokine responses may be associated with genetic polymorphisms of the milk proteins. Concentration was lower for caprine apart from the group of patients investigated; in particular, HL-EC groups demonstrated a lower secretion in the blood stream of the interleukin. Concentrations of IL-6 were higher in cultured PBMC incubated with α S2-CN from bovine and ovine milks than in that from caprine milk. In particular, the β -CN fraction induced the highest levels of TNF- α in ovine and caprine milk, whereas the α S2- CN fraction from bovine milk stimulated the highest level of IL-6 and played a major role in production of IL-1 β from cultured PBMC. In epileptic children having high cytokine levels than those of control children, the protein fraction of milk able to modulate the secretion of inflammatory interleukins appears to be represented by alpha s2 casein. Results of these recent works highlight how much the understanding of the effects of complex food matrices such as milk is still far from being completely revealed.

Caption to **Table 1**. Children have been grouped according to the level of cytokines compared to the level found in blood from control patients, as follows: LL-EC group of children with epilepsy having levels of cytokines comparable to those of

Interleukin	Bovine milk	Caprine milk	Ovine milk
TNF- α , pg./mL	284.72 $\pm$ 9.33	329.78 $\pm$ 8.14	336.40 $\pm$ 8.42
IL-1 β , pg./mL	58.01 $\pm$ 1.02	50.44 $\pm$ 0.92	53.44 $\pm$ 1.06
IL-6, pg./mL	1,347.86 $\pm$ 28.81	1,245.12 $\pm$ 26.89	1,266.38 $\pm$ 30.01

Adapted from Albenzio et al. [4].

Table 1.
Mean level of TNF- α , IL-10, IL-6, and IL-1 β in PBMC from blood of children with generalized epilepsy, incubated with 100 μ g/mL of κ -CN, α S1-CN, α S2-CN, β -CN, and a mix of α -LA and β -LG obtained from bovine, caprine, and ovine milks.

control group (low level); ML-EC group of children with epilepsy with cytokine levels at least 5-fold higher (medium levels) than those of the control group; HL-EC group of children with epilepsy having cytokine levels at least 10-fold higher (high levels) than those of control group.

In studies regarding childhood epilepsy, it is noteworthy to investigate the onset of oxidative stress following milk feeding, as it contributes to acute injury-induced neuronal damage [24].

The evaluation of stimulation of cultured PMBC with milk and protein fractions from different species on ROS/RNS levels, evidenced that caprine milk was able to mitigate the effect on oxidative stress than bovine and ovine milks. Furthermore, within caprine milk protein fractions the ROS/RNS levels were found comparable. Lower levels of ROS/RNS detected in PBMC cultured with caprine milk fraction could be related to the lower levels of TNF- α in the corresponding fraction.

It has recently been reported that the neuronal damage generated by acute injuries, resulting in detrimental effects on areas of the brain associated with learning and memory function, may be partially due to oxidative damage, which occurs during epileptogenesis [24]. Those authors also suggested that a combination therapy, based on antioxidants and antiseizure drugs, might help to reduce the cognitive impairment as comorbidities occurring in epileptic patients.

4. Lipid fraction in caprine milk

Milk fat derived from small ruminants represents a valuable source of fatty acids, from a nutritional and health point of view [25].

Small ruminants' milk fat presents high content in medium-chain fatty acids (C6–C10; MCFA) and five fatty acids (C10:0, C14:0, C16:0, C18:0, and C18:1), accounting for >75% of total fatty acids in caprine and ovine milk. In fact, levels of the MCFA as caproic (C6:0) (2.4%, 1.6%), caprylic (C8:0) (2.7%, 1.3%), capric (C10:0) (10.0%, 3.0%), and lauric (C12:0) (5.0%, 3.1%) are significantly higher in goat than in cow milk, respectively [26].

During digestion, MCFA are more susceptible to the action of digestive enzymes, thanks to their low molecular weight and water solubility. Gastric lipase plays a particularly important role, as it promotes faster and more complete hydrolysis than in long-chain fatty acids. Hydrolysis of MCFA releases free fatty acids which can then be absorbed without being re-esterified in intestinal cells. MCFA have been used in the treatment of some metabolic diseases; Sanz Sampelayo et al. [25] reported that some patients suffering from malabsorption problems, pancreatic insufficiency, deficiency of bile salts or subject to intestinal resection have been treated with capric and caprylic acid. Derivatives of caprylic and capric acid were emphasized as medical and nutritional specialties: MCFA were suggested as tools in the control of obesity, in lowering serum cholesterol, in infant feeding and in the treatment of childhood epilepsy. Furthermore, some studies show antimicrobial and antiviral activity for C8: 0, C10: 0 and C12: 0 [27], in particular lauric acid has been studied for its antimicrobial activity against *Helicobacter pylori* [28].

The fat component of milk also contains essential nutrients, such as vitamins (A, D, E, K) or their precursors (carotenoids), essential polyunsaturated fatty acids and isomers of conjugated linoleic acid (CLA), which humans are not able to synthesize. CLA are a group of positional and geometric isomers of linoleic acid (cis9, cis12-C18:2, n-6). The isomer cis9, trans11-CLA, named rumenic acid, is the most prevalent—75–80% of the total CLA content in milk and meat [29]. CLA accounted for 2–4%, calculated as a percentage of total fatty acids esterified in phospholipids, in caprine and ovine milk, and less than 1% in bovine milk [30].

Dairy products naturally contain CLA and vaccenic acid (VA) as they are produced in the rumen. The CLA content in milk is influenced by numerous factors, both endogenous (animal breed, genetic type, lactation stage and pregnancy) and exogenous (diet and environmental conditions).

Diet represents the factor that most influences milk CLA content, which can be naturally enriched by fresh pasture feeding [31], or through the use of specific dietary formulations including oilseeds or fish oil [32]. The content of CLA, VA and α -linolenic acid (ALA) in milk, cheese and meat are profoundly influenced by the diet of animals, which is the major source of variation. The use of pasture, fresh forage and specific vegetable fat supplements in the sheep diet greatly influences the content of these compounds in sheep products [33].

In the Mediterranean area, grazing represents a fundamental dietary strategy in improving the health component of fatty acids present in sheep's milk and meat. In fact, the meat and milk of grass-fed ruminants are characterized by a higher content of CLA, omega-3 fatty acids, beta-carotene and vitamins A and E than the meat and milk of animals fed indoors. Green herbs are particularly rich in polyunsaturated fatty acids, especially ALA, which have a positive effect on the content of C18: 3n-3, VA and CLA in milk and meat. ALA in the rumen undergoes a partial biohydrogenation at VA, in animal tissues is then partially converted into cis-9, trans-11 CLA, thanks to the intervention of $\Delta 9$ -desaturase. Fish oil was used in the diet of goats resulting in a significant increase in the rate of transfer of dietary EPA and DHA into milk [34]. Recently, CLA and VA have acquired substantial importance as a consequence of the encouraging results in human studies [35].

Biochemical studies showed beneficial effects of the cis-9, cis-11 CLA on neoplastic and atherosclerotic processes [36, 37] as well as a cholesterol-lowering effect [35]. Epidemiological studies showed that C18:3n3 is associated with a reduced risk of cardiovascular diseases [38], whereas EPA and DHA have beneficial effects on proper brain and visual development in the fetus, and maintenance of neural and visual tissues throughout life [39].

In different studies it has been shown that CLA, being an efficient ligand of PPAR alpha, is able to activate the peroxisomal beta oxidation [40] required for the synthesis of DHA starting from ALA. In addition, the peroxisomal beta oxidation is also the catabolic pathway of oxygenated eicosanoids [41], thus carrying out an anti-inflammatory activity. It follows that the diet should be rich in CLA and VA in order to increase the biosynthesis of DHA and the presence of fatty acids of the omega-3 series among highly unsaturated fatty acids (HUFA). Furthermore, CLA is metabolized in a similar way to linoleic and is able to decrease the formation and incorporation of arachidonic acid, contributing to the increase of the n-3 HUFA score.

4.1 Role of caprine milk in infant metabolic disorders

According to data provided by the World Health Organization (WHO), the number of obese people in the world has tripled since 1975. Obesity and overweight are now recognized as real public health problems in every part of the world [42].

The first cause of obesity and overweight is an energy imbalance between calories consumed and calories expended, which is mainly due to an increased intake of energy-dense foods rich in fat and to physical inactivity due to the sedentary nature of many forms of work and to the enhancement of urbanization. Overweight and obesity are strictly related to the insurgence of many other diseases affecting human health, represented by cardiovascular diseases, diabetes, musculoskeletal disorders, and some types of cancers.

In recent decades, pediatric research has focused on finding a relationship between childhood obesity and infant nutrition in the first six months of life [43]. In fact, in the period between the final stages of fetal growth and the first months of the newborn life, preadipocyte cells develop in mature adipose tissue, driven by hormonal and nutritional stimuli. Childhood obesity appears to be associated with an increased risk of obesity, premature death, and disability in adulthood. Furthermore, obese children exhibit breathing difficulties, increased risk of fractures, hypertension, early markers of cardiovascular disease, insulin resistance, and psychological distress.

Until recently, adipose tissue was considered only an energy reserve organ, but, following the increasing diffusion of obesity, researchers have focused attention in this field over the past twenty years [44], coming to the consideration that adipose tissue does not represent only an energy reserve, but is an important endocrine organ that has numerous targets, including some areas of the brain such as the hypothalamus. Adipose tissue is also involved in the regulation of many processes, such as homeostasis of fat mass and nutrients, regulation of the immune response, control of blood pressure, thyroid and reproductive system functions [45].

Obesity is a metabolic disorder that manifests itself in two phenomena, namely the increase in the number of adipocytes, due to hypertrophic phenomena, and an abnormal lipid filling of already existing adipocytes, caused by hyperplastic phenomena [46]. Hyperplasia occurs mainly in the developmental age, while hypertrophy in adulthood. Obesity starts with an excessive energetic intake, due to the ingestion of fats and carbohydrates, which induces mature adipocytes to store the excess of energy as triglycerides that accumulated within the adipocytes cells, thus activating the adipogenesis with consequent growth of the cells in size and number. This cellular transformation causes a change in the adipokines secretion, the activation of pro-inflammatory processes and the increase of oxidative stress phenomena [47].

Infant diet is able to influence the development of adipose tissue in adults, because the transformation of preadipocyte cells into mature adipocytes takes place during the last stages of fetus growth and the first months of newborn life. Being milk the only food taken by the newborn in these phases, many researchers are interested to study the effects of milk fat component, particularly fatty acids, on the adipose tissue.

Flachs et al. [48] observed that some n-3 series LC-PUFAs (polyunsaturated fatty acids), as EPA (eicosapentaenoic acid) and DHA (docosahexaenoic), can exert a metabolic action on adipose tissue to prevent obesity. Some authors have tested the effect of MUFAs (monounsaturated fatty acids) and CLAs (conjugated linoleic acid) as herbal extracts for obesity [49]. Guo et al. [50] have shown that caprylic acid and MCFA (medium chain fatty acids) have the ability to inhibit the synthesis of triglycerides by adipocytes. Other authors have also observed a relationship between fatty acid composition of diet and childhood obesity, evidencing synergistic effects among different fatty acids; in particular the association of n-6 series PUFAs with high concentrations of LA (linoleic acid) and of ALA (alpha-linolenic acid) seems to support growth of adipose tissue under nutritional *stimuli* [51]. However, both the quantity and quality of fatty acids that reach the adipose tissues are influenced by the biochemical processes during digestion [52].

It is therefore interesting to understand the effect of the digestive process on milk fatty acids bioavailability, and whether this process may influence adipose tissue. Caprine milk was compared to human and formula milk to evaluate the effect of *in vitro* digestion on mature adipocytes, paying particular attention to the role of milk fatty acid composition [5]. Digested caprine milk source exhibited

a reduced cellular 3 T3-L1 viability due to activation of apoptotic phenomena. Apoptosis is an important biological process by which the body removes aged cells during physiological or pathological conditions [53], avoiding eliciting inflammation. Moreover, digested human and formula milk induced lower oxidative stress in mature adipocytes evidenced by lower levels of ROS than caprine milk digested sample probably due to the peculiar free fatty acids profile of different milk sources.

The role of ROS in adipose tissue is complex. In preadipocytes the accumulation of mitochondrial ROS could inhibit cell proliferation [54], whereas in mature adipocytes from obese rats high level of ROS were observed and protection of adipocytes from oxidative stress is recognized as a potential clinical strategy in obesity treatment [55].

Caprilic acid has been shown to induce ROS generation and might also modulate PPAR γ activity indirectly via the ROS signaling pathways [50]. Accordingly, digested milk from caprine showed a mean content of free caprilic acid higher than FM and HM (5.17 $\mu\text{g/ml}$ for caprine, vs. 4.85, 3.5 $\mu\text{g/ml}$ of extract for formula and human milk respectively), and this could partly explain the lower ROS content in digested human and formula. On the other hand, many natural lipid compounds with anti-inflammatory and antioxidant effects have been used to treat obesity such as n-3 PUFA, EPA and DHA, MUFA and CLA [49]. Santillo et al. [5] observed a higher content of free oleic and linoleic acid in digested human milk and infant formula; oleic acid content 1.5 and 6-folds higher and linoleic acid content 2 and 5.5-folds higher than what observed in ruminant milk, respectively. Since ROS are key signaling molecules that play an important role in the progression of inflammatory disorders [56], NF- κB p65 and HMGB1 were evaluated. HMGB1 promotes inflammation and its receptors interact with NF- κB p65 forming a positive feedback loop to sustain inflammatory conditions [57]. Among treatments, the lowest gene expression was found in HM and CM, the highest in FM.

5. Conclusions

Goat milk has received increasing attention due to its composition, in particular for feeding of fragile categories such as infants and the elderly.

Goat milk protein fraction revealed the presence of a high number of alleles at the four casein loci, associated with different levels of casein synthesis into milk. Recent research evidenced the important role of goat milk protein fraction in eliciting hypoallergenic reaction and in triggering cytokine response in cow milk allergy and infant epilepsy, respectively.

Moreover the exploitation of caprine milk in infant nutrition, in particular cases of pediatric metabolic disorders, should further investigate the role of the acidic profile of such milk on the mechanisms of both adipocyte differentiation and pro-inflammatory *stimulus*.

The role of goat's milk as a nutritional intervention useful to support clinical therapies in some emerging pediatric diseases shows promising results thus deserves further research.

IntechOpen

IntechOpen

Author details

Marzia Albenzio*, Francesca d'Angelo and Antonella Santillo
Department of Agriculture, Food, Natural Resources and Engineering (DAFNE),
University of Foggia, Foggia, Italy

*Address all correspondence to: marzia.albenzio@unifg.it

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] FAOSTAT, 2021 accessed January 27, 2021.
- [2] Albenzio M, Campanozzi A, D'Apolito M, Santillo A, Pettoello Mantovani M, Sevi A. Differences in protein fraction from goat and cow milk and their role on cytokine production in children with cow's milk protein allergy. *Small Ruminant Research*. 2012;105:202-205. DOI: 10.1016/j.smallrumres.2012.02.018.
- [3] Albenzio M, Santillo A, Ciliberti MG, Figliola L, Caroprese M, Marino R, Polito AN. Milk from different species: Relationship between protein fractions and inflammatory response in infant affected by generalized epilepsy. *Journal of Dairy Science*. 2016;99:5032-5038. DOI: 10.3168/jds.2015-10704.
- [4] Albenzio M, Santillo A, Ciliberti MG, Figliola L, Caroprese M, Polito AN, Messina G. Milk nutrition and childhood epilepsy: An ex vivo study on cytokines and oxidative stress in response to milk protein fractions. *Journal of Dairy Science*. 2018;101(6):4842-4852. DOI: 10.3168/jds.2017-13104.
- [5] Santillo A, Figliola L, Caroprese M, Marino R, d'Apolito M, Giardino I and Albenzio M. Effect of lipid fraction of digested milk from different sources in mature 3T3-L1 adipocyte. *Journal of Dairy Research*. 2019. DOI: 10.1017/S0022029919000104
- [6] Bonanno A, Di Grigoli A, Montalbano M, Bellina V, Mazza F, Todaro M. Effects of diet on casein and fatty acid profiles of milk from goats differing in genotype for α S1-casein synthesis. *European Food Research and Technology*. 2013;237:951-963.
- [7] Cebo C, Lopez C, Henry C, Beauvallet C, Me'nard O, Bevilacqua C, Bouvier F, Caillat H, Martin P. Goat α S1-casein affects milk fat globule physicochemical properties and the composition of the milk fat globule membrane. *Journal of Dairy Science*. 2012;95:6215-6229. DOI: 10.3168/jds.2011-5233.
- [8] Haenlein GFW. Goat milk in human nutrition. *Small Ruminant Research*. 2004;51(2):155-163. DOI: 10.1016/j.smallrumres.2003.08.010.
- [9] Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, Siegert S, Dubakiene R, Rudzeviciene O, Reche M, Fiandor A, Papadopoulos NG, Malamitsi-Puchner A, Fiocchi A, Dahdah L, Sigurdardottir ST, Clausen M, Stańczyk-Przyłuska A, Zeman K, Mills EN, McBride D, Keil T, Beyer K. Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. *Allergy*. 2015;70:963-972. DOI: 10.1111/all.12630.
- [10] Park YW. Bioactive components of goat milk, In: Park YW. (Ed). *Bioactive Components in Milk and Dairy Products*: Wiley-Blackwell Publishers Ames, Iowa and Oxford, England; 2009. p. 43-82.
- [11] Natale M, Bisson C, Monti G, Peltran A, Perono Garoffo L, Valentini S, Fabris C, Bertino E, Coscia A, Conti A. Cow's milk allergens identification by two-dimensional immunoblotting and mass spectrometry, *Molecular Nutrition and Food Research*. 2004;48:363-369. DOI: 10.1002/mnfr.200400011.
- [12] Tiemessen MM, van Ieperen-Van Dijk AG, Bruijnzeel-Koomen CAFM, Garssen J, Knol EFK, Van Hoffen EV. Cow's milk-specific T-cell reactivity of children with and without persistent cow's milk allergy: key role for IL-10, J. *Allergy Immunology*. 2003;5:932-939. DOI: 10.1016/j.jaci.2003.12.016.

- [13] Armaforte E, Curran E, Huppertz T, Ryan CA, Caboni MF, O'Connor PM, Ross RP, Hirtz C, Sommerer N, Chevalier F, Kelly AL. Proteins and proteolysis in pre-term and term human milk and possible implications for infant formulae. *International Dairy Journal*. 2010;20:715-723. DOI: 10.1016/j.idairyj.2010.03.008.
- [14] Lönnerdal B. Nutritional and physiological significance of human milk proteins, *American Journal of Clinical Nutrition*. 2003;77:1537-1543. DOI: 10.1093/ajcn/77.6.1537S.
- [15] Høst A, Halcken S. Hypoallergenic formulas—when, to whom and how long: after more than 15 years we know the right indication! *Allergy*. 2004;59(s78): 45-52. DOI: 10.1111/j.1398-9995.2004.00574.x.
- [16] Korhonen H, Pihlanto A. Bioactive peptides: production and functionality. *International Dairy Journal*. 2006;16:945-960. DOI: 10.1016/j.idairyj.2005.10.012.
- [17] Santillo A, Kelly AL, Palermo C, Sevi A, Albenzio M. Role of indigenous enzymes in proteolysis of casein in caprine milk. *International Dairy Journal*. 2009;19:655-660. DOI: 10.1016/j.idairyj.2009.06.011.
- [18] Li G, Bauer S, Novak M, Norwood B, Rosenow B, Knake S, Oertel WH, Hamer HM. Cytokines and epilepsy. *Seizure*. 2011;20:249-256. DOI: 10.1016/j.seizure.2010.12.005.
- [19] Youn Y. The role of cytokines in seizures: Interleukin (IL)-1 β , IL-1Ra, IL-8, and IL-10. *Korean Journal of Pediatrics*. 2013;56:271-274. DOI: doi: 10.3345/kjp.2013.56.7.271.
- [20] O'Garra A, Barrat FJ, Castro AG, Vicari A, Hawrylowicz C. Strategies for use of IL-10 or its antagonists in human disease. *Immunology Reviews*. 2008;223:114-131. DOI: 10.1111/j.1600-065X.2008.00635.x
- [21] Vezzani A, Baram TZ. New roles for interleukin-1 beta in the mechanism of epilepsy. *Epilepsy Currents*. 2007;7: 45-50. DOI: 10.1111/j.1535-7511.2007.00165.x.
- [22] Vezzani A, Balosso S, Ravizza T. The role of cytokines in the pathophysiology of epilepsy. *Brain Behavior and Immunity*. 2008;22:797-803. DOI: 10.1016/j.bbi.2008.03.009.
- [23] Samland H, Huitron-Resendiz S, Masliah E, Criado J, Henriksen SJ, Campbell IL. Profound increase in sensitivity glutamatergic but not cholinergic agonist induced seizures in transgenic mice with astrocyte production of IL-6. *Journal of Neuroscience Research*. 2003;73:176-187. DOI: 10.1002/jnr.10635.
- [24] Pearson JN, Rowley S, Liang LO, White AM, Day BJ, Patel M. Reactive oxygen species mediate cognitive deficits in experimental temporal lobe epilepsy. *Neurobiology of Disease*. 2015;82:289-297. DOI: doi: 10.1016/j.nbd.2015.07.005.
- [25] Sanz Sampelayo MR, Chilliard Y, Schmidely P, Boza J. Influence of type of diet on the fat constituents of goat and sheep milk, *Small Ruminant Research*. 2007;68:42-63. DOI: 10.1016/j.smallrumres.2006.09.017.
- [26] Park YW, Juárez M, Ramos M, Haenlein GFW. Physico-chemical characteristics of goat and sheep milk. *Small Ruminant Research*. 2007;68:88-113. DOI: 10.1016/j.smallrumres.2006.09.013.
- [27] Germa JB, Dillard CJ. Saturated fats: a perspective from lactation and milk composition, *Lipids*. 2010;45:915-923. DOI: doi: 10.1007/s11745-010-3445-9.
- [28] Sun CQ, O'Connor CJ, Robertson AM. Antibacterial action of fatty acids and monoglycerides against *Helicobacter pylori*. *FEMS Immunology*

and Medical Microbiology. 2003;36:9-17. DOI: 10.1016/S0928-8244(03)00008-7.

[29] Schmid A, Collomb M, Sieber R, Bee G. Conjugated linoleic acid in meat and meat products: a review. *Meat Science*. 2006;73:29-41. DOI: 10.1016/j.meatsci.2005.10.010.

[30] Contarini G, Pelizzola V, Povo M. Content of conjugated linoleic acid in neutral and polar lipid fractions of milk of different ruminant species, *International Dairy Journal*. 2009;19:342-344. DOI: 10.1016/j.idairyj.2008.10.013.

[31] Bauman DE, Corl BA, Peterson GP. The biology of conjugated linoleic acids in ruminants, In: Sebedio J.L., Christie W.W. and Adlof R., (Eds.). *Advances in Conjugated Linoleic Acid Research* vol. 2. AOCS Press; Champaign, IL, USA, 146-173; 2003.

[32] Collomb M, Schmid A., Sieber R, Wechsler D, Ryhanen E. Conjugated linoleic acid in milk fat: variation and physiological effects. *International Dairy Journal*. 2006;16:1347-1361. DOI: 10.1016/j.idairyj.2006.06.021.

[33] Nudda A, Battacone G, Bonaventura ON, Cannas A, Francesconi AHD, Atzori AS, Pulina G. Feeding strategies to design the fatty acid profile of sheep milk and cheese. *Revista Brasileira de Zootecnia*. 2014;43:445-456. DOI: 10.1590/S1516-35982014000800008.

[34] Kitessa SM, Gulati SK, Ashes JR, Fleck E, Scott TW, Nichols PD. Utilization of fish oil in ruminants II. Transfer of fish oil fatty acids into goats' milk, *Animal Feed Science and Technology*. 2001;89:201-208. DOI: 10.1016/S0377-8401(00)00232-7.

[35] Pintus S, Murru E, Carta G, Cordeddu L, Batetta B, Accossu S, Pistis D, Uda S, Ghiani ME, Mele M,

Secchiari P, Almerighi G, Pintus P, Banni S. Sheep cheese naturally enriched in alpha-linolenic, conjugated linoleic and vaccenic acids improves the lipid profile and reduces anandamide in the plasma of hypercholesterolaemic subjects. *British Journal of Nutrition*. 2013;109:1453-1462. DOI: 10.1017/S0007114512003224.

[36] Bhattacharya A, Banu J, Rahaman M, Causey J, Fernandes G. Biological effects of conjugated linoleic acids in health and disease. *The Journal of Nutritional Biochemistry*. 2006;17:789-810. DOI: 10.1016/j.jnutbio.2006.02.009.

[37] Sofi F, Buccioni A, Cesari F, Gori AM, Minieri S, Mannini L, Casini A, Gensini GF, Abbate R, Antongiovanni M. Effects of a dairy product (pecorino cheese) naturally rich in cis-9, trans-11 conjugated linoleic acid on lipid, inflammatory and haemorheological variables: a dietary intervention study. *Nutrition, Metabolism and Cardiovascular Diseases*. 2010;20:117-124. DOI: 10.1016/j.numecd.2009.03.004.

[38] Roth EM, Harris WS. Fish oil for primary and secondary prevention of coronary heart disease. *Currents Atherosclerosis Reports*. 2010;12:66-72. DOI: 10.1007/s11883-009-0079-6.

[39] Ruxton C. Health benefits of omega-3 fatty acids. *Nursing Standard*. 2004;18(48):38-42. DOI: doi: 10.7748/ns2004.08.18.48.38.c3668.

[40] Banni S, Petroni A, Blasevich M, Carta G, Angioni E, Murru E, Day BW, Melis MP, Spada S, Ip C. Detection of conjugated C16 PUFAs in rat tissues as possible partial beta-oxidation products of naturally occurring conjugated linoleic acid and its metabolites. *Biochimica et Biophysica Acta*. 2004;1682:120-127. DOI: 10.1016/j.bbalip.2004.03.003.

- [41] Ferdinandusse S, Meissner T, Wanders RJ, Mayatepek E. Identification of the peroxisomal beta-oxidation enzymes involved in the degradation of leukotrienes. *Biochemical and Biophysical Research Communications*. 2002;293:269-273. DOI: 10.1016/S0006-291X(02)00214-0.
- [42] <https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight> - Access date: 07.01.2019
- [43] Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet*. 2010;375:1737-1748. DOI: 10.1016/S0140-6736(10)60171-7.
- [44] Bray GA, Bellanger T. Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. *Endocrine*. 2006;29:109-117. DOI: 10.1385/ENDO:29:1:109.
- [45] Grant RW, Dixit VD. Adipose tissue as an immunological organ. *Obesity* 2015.;23(3):512-518. DOI: 10.1002/oby.21003.
- [46] Berry R, Jeffery E, Rodeheffer MS. Weighing in on adipocyte precursors. *Cell Metabolism*. 2014;19:8-20. DOI: 10.1016/j.cmet.2013.10.003.
- [47] Baret P, Septembre-Malaterre A, Rigoulet M, d'Hellencourt CL, Priault M, Gonthier MP, Devin A. Dietary polyphenols preconditioning protects 3T3-L1 preadipocytes from mitochondrial alterations induced by oxidative stress. *The international Journal of Biochemistry & Cell Biology*. 2013;45:167-174. DOI: 10.1016/j.biocel.2012.10.007.
- [48] Flachs P, Rossmeisl M, Bryhn M, Kopecky J. Cellular and molecular effects of n-3 polyunsaturated fatty acids on adipose tissue biology and metabolism. *Clinical Science*. 2008;116:1-16. DOI: 10.1042/CS20070456.
- [49] Chang WT, Wu CH, Hsu CL. Diallyl trisulphide inhibits adipogenesis in 3T3-L1 adipocytes through lipogenesis, fatty acid transport, and fatty acid oxidation pathways. *Journal of Functional Foods*. 2015;16:414-422. DOI: 10.1016/j.jff.2015.05.002.
- [50] Guo W, Xie W, Han J. Modulation of adipocyte lipogenesis by octanoate: involvement of reactive oxygen species. *Nutrition & Metabolism*. 2006;3:30. DOI: 10.1186/1743-7075-3-30.
- [51] Ailhaud G, Guesnet P. Fatty acid composition of fats is an early determinant of childhood obesity: a short review and an opinion. *Obesity reviews*. 2004;5:21-26. DOI: 10.1111/j.1467-789x.2004.00121.x.
- [52] Devle H, Ulleberg EK, Naess-Andresen CF, Rukke EO, Vegarud GE, Ekeberg D. Reciprocal interacting effects of proteins and lipids during ex vivo digestion of bovine milk. *International Dairy Journal*. 2014;36:6-13. DOI: 10.1016/j.idairyj.2013.11.008.
- [53] Sergeev IN. 1, 25-Dihydroxyvitamin D 3 induces Ca²⁺-mediated apoptosis in adipocytes via activation of calpain and caspase-12. *Biochemical and biophysical research communications*. 2009;384:18-21. DOI: 10.1016/j.bbrc.2009.04.078.
- [54] Wang X, Hai C. Redox modulation of adipocyte differentiation: hypothesis of "Redox Chain" and novel insights into intervention of adipogenesis and obesity, *Free Radical Biology and Medicine*. 2015;89:99-125. DOI: 10.1016/j.freeradbiomed.2015.07.012.
- [55] Kusunoki C, Yang L, Yoshizaki T, Nakagawa F, Ishikado A, Kondo M, Morino K, Sekine O, Ugi S, Nishio Y, Kashiwagi A, Maegawa H. Omega-3 polyunsaturated fatty acid has an anti-oxidant effect via Nrf-2/HO-1 pathway in 3T3-L1 adipocytes.

Biochemical and Biophysical Research
Communication. 2013;430:225-230.
DOI: 10.1016/j.bbrc.2012.10.115.

[56] Mittal M, Siddiqui MR, Tran K,
Reddy SP, Malik AB. Reactive oxygen
species in inflammation and tissue
injury Antioxidants & Redox Signaling.
2014;20:1126-1167. DOI: 10.1089/
ars.2012.5149.

[57] Wang AS, Xu CW, Xie HY, Yao AJ,
Shen YZ, Wan JJ, Zhang HQ, Fu JF,
Chen ZM, Zou ZQ, Li D, Zhang XH.
DHA induces mitochondria-mediated
3T3-L1 adipocyte apoptosis by down-
regulation of Akt and ERK. Journal of
Functional Foods. 2016;21:517-524. DOI:
doi.org/10.1016/j.jff.2016.01.001.