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## Milk: Past and Present

S Bulajić<sup>1\*</sup>, J Đorđević<sup>1</sup>, T Ledina<sup>1</sup>, D Šarčević<sup>2</sup> and M Ž Baltić<sup>1</sup>

<sup>1</sup> Department of Food Hygiene and Technology, Faculty of Veterinary Medicine, Bulevar oslobođenja 18, 11 000 Belgrade, Serbia

<sup>2</sup> Institute of Meat Hygiene and Technology, Kaćanskog 13, 11 000 Belgrade, Serbia

Email: snezab@vet.bg.ac.rs

**Abstract.** Although milk/dairy consumption is part of many cultures and is recommended in most dietary guidelines around the world, its contribution to overall diet quality remains a matter of controversy, leading to a highly polarized debate within the scientific community, media and public sector. The present article, at first, describes the evolutionary roots of milk consumption, then reviews the milk-derived bioactive peptides as health-promoting components. The third part of the article, in general, presents the associations between milk nutrients, disease prevention, and health promotion.

### 1. Milk revolution

Humans have used animal milk as a food resource for at least 8500 years. Despite the significant effort of the scientific community, the clear picture of how, where, and when humans initially consumed milk has not been obtained. However, scientists have revealed the very interesting story of the so-called milk revolution [1]. The main premise of this story is that milk consumption is a classic example of how culture has shaped the human genome, or scientifically speaking, created a gene-culture evolution.

As farming started to replace hunting and gathering in the Middle East around 11000 years ago, adoption of animal milk consumption by humans required behavioral adaptations, such as culturing and curdling techniques in order to remove or reduce the lactose content and thereby make dairy products digestible. Otherwise, milk was essentially a toxin to adults because they could not synthesize the lactase enzyme required for lactose degradation. Archaeological findings undoubtedly have proved this first step in the milk revolution. In the 1970s, archaeologist Petar Bogucki, while he was excavating a Stone Age site in central Poland, found a fragment of pottery dotted with tiny holes. He presumed that the pottery might be connected with cheese-making, but at that time, he had no idea how to test his hypothesis. Fortunately, the mysterious pottery was properly stored until 2011, which gave Melanie Roffet-Salque the chance to analyze fatty residues preserved in the clay. The analysis showed the signatures of abundant milk fats, which served as evidence that the early Polish farmers had used the pottery as sieves, trying to separate milk solids from liquid whey [2].

In terms of evolutionary biology, persistent milk consumption is regarded as a novel dietary behavior established by genetic mutation. Lactose tolerance is a classic example of selection-driven evolutionary change in humans from milk-drinking cultures [3]. The trait of lactase persistence (LP) in humans seems to be linked to a single nucleotide in which the DNA base cytosine changed to thymine in a genomic region not far from the lactase gene. According to Itan and his colleagues [4], this genetic mutation spread through Europe about 7500 years ago from the broad, fertile plains of Hungary.



Once the LP allele appeared, it offered a major selective advantage, as it opened up a valuable new source of nutrition. However, the effects were not confined just to a more varied diet. Interestingly, researchers estimated that people with the mutation were more successful in reproduction and would have produced up to 19% more fertile offspring in comparison to those who lacked the new allele [4]. So, taken altogether, gene-culture coevolution began to happen or as Thomas said figuratively, “the practice of dairying and LP allele feed off of each other” [4]. A novel selection pressure was created, favoring genes that extended lactase production into adulthood, especially in populations with long pastoralist traditions that independently evolved lactase persistence – in Europe India, East Africa, and the Arabian Peninsula. According to research results [5], the degree of selection was among the strongest seen to date for any gene in the human genome. However, given that dairying in the Middle East started thousands of years before the LP allele emerged in Europe, the ancient European herders had to find a way to reduce the lactose content of the milk from their animals. Therefore, in this region, the cultural transmission of dairying practice was followed relatively rapidly by the evolution of technological know-how for processing milk into cheese and yogurt. Thus, the selective advantage was not seen, as any adult could obtain nutritional benefits from milk by consuming dairy products. In these populations, adaptive cultural evolution overcame the natural selection acting in the genes. By the late Neolithic and early Bronze Ages, around 5000 years ago, the LP allele was established in most of the northern and central European human populations.

Beja-Pereira and co-workers [6] also argued the coevolutionary hypothesis. The authors found a substantial geographic coincidence between cattle milk protein gene diversity, present-day lactose tolerance in Europeans and the distribution of the Neolithic cattle farming sites. The study results supported the hypothesis that selection driven by the advantages of milk consumption concurrently influenced the frequencies of milk protein genes in cattle and lactase gene in humans [6]. Furthermore, genetic data from another study confirmed archaeological evidence suggesting that the early cattle herders in North-Central Europe were dependent on milk [7]. The presumption that Neolithic cattle herds were managed for early weaning of calves is supported by analysis of intra-tooth changes in nitrogen isotope ratios from archaeological cattle teeth remains.

Although LP is hailed as one of clearest examples of gene-culture coevolution in humans [8], it offers only indirect lines of evidence. Warinner et al. [9] reported the first direct evidence of milk consumption, by identifying the whey protein,  $\beta$ -lactoglobulin (BLG), preserved in human dental calculus from the Bronze Age (ca. 3000 BCE). Therefore, BLG, as a specific milk biomarker, enabled scientists in this field the opportunity to detect complex patterns of milk consumption.

## 2. Milk-derived bioactive peptides

Bioactive peptides are described as “food components (genuine or generated) that, in addition to their nutritional value, retain many biological properties and exert a physiological effect in the body” [10]. Mellander first reported that ingestion of casein-derived phosphorylated peptides led to enhanced vitamin D-independent calcification in rachitic infants [11]. Since then, a number of food-derived components isolated from various sources (e.g. eggs, bovine blood, collagen, gelatin, various fish species) [12] have been proposed as being bioactive. Nevertheless, bovine milk, especially the milk proteins, is currently the main source of bioactive peptides. Milk-derived bioactive peptides are usually kept inactive within the primary structure of milk protein, and proteolysis is required for their release and activation to exert a physiological response. Generation of the bioactive peptides can occur in the following ways:

- a) enzymatic hydrolysis *in vivo* during digestion by digestive enzymes like pepsin, trypsin, chymotrypsin etc., or gut microbial enzymes
- b) fermentation of milk with proteolytic lactic acid bacteria (LAB) during milk processing or ripening
- c) *in vitro* hydrolysis using isolated enzymes

Numerous beneficial health effects have been attributed to known milk peptide sequences, including antihypertensive, antithrombotic, anti-inflammatory, antioxidative, antimicrobial, opioid, mineral binding (casein phosphopeptides – CPPs), cytomodulatory, immunomodulatory and anti-obesity properties [13-16]. In particular, the cardiovascular system is the main target of milk-derived bioactive peptides, and the blood pressure-reducing peptides that inhibit the angiotensin-converting enzyme I (ACE) are the most widely studied. Antihypertensive properties have been attributed, in particular, to two potent inhibitory tripeptides from bovine casein (casokinins), Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP), primarily isolated from sour milk fermented with *Lactobacillus helveticus* and *Saccharomyces cerevisiae* [17]). ACE-inhibitory peptides such as  $\alpha$ -lactorphin and  $\beta$ -lactorphin are generated from the whey proteins  $\alpha$ -lactalbumin and lactoglobulin, respectively [18]. The ACE-inhibitory peptides, IPP and VPP, most likely resist digestion *in vivo* due to the presence of a proline residue at the carboxyl terminal end, which is resistant to the action of Pro-specific peptidases. Antihypertensive peptides influence blood pressure by preventing ACE from synthesizing the vasoconstrictor, angiotensin II, as well as preventing the enzymatic degradation of bradykinin, a vasodilator, but also through mechanisms that are independent of ACE inhibition such as vascular release of endogenous vasodilators (e.g. prostaglandin I<sub>2</sub>, nitric oxide, and carbon monoxide).

Likewise, yogurt bacteria, cheese starter bacteria, commercial probiotic bacteria as well as non-starter LAB have been demonstrated to produce potent bioactive peptides, through their proteolytic activity. It is noteworthy that the specific peptidase activity of LAB affects the bioactivity of the peptides produced [19]. Interestingly, increased ACE-inhibitory activity has been demonstrated in milk fermented by the mutants of *L. helveticus* CNRZ32 lacking both general aminopeptidase and X-prolyl dipeptidyl aminopeptidase [20]. In that study, it was suggested that both peptidases are involved in the release or degradation of ACE-inhibitory peptides during the fermentation. Undoubtedly, identification of the links between the proteolytic pattern of LAB cultures used in dairy fermentation and resulting milk bioactivity is of the utmost importance.

The physiological effect is not solely linked to the bioactive peptides released by proteolysis. The protein fraction naturally present in milk fat globule membrane (in particular, fatty acid binding protein and glycoprotein), have been demonstrated to exert anti-cancer and antimicrobial properties [21].

As we are witnessing the post-genomics era, molecular studies are needed to assess the underlying mechanisms by which bioactive peptides exert their physiological effects. In this context, nutrigenomics is a promising tool, and by its definition underscores the basic fact that food components can interact with the genome and consequently can influence human health. The ability to moderate the gene expression should be considered one of the major hallmarks of bioactive peptides.

### 3. Milk and health

The main concern about possible negative effects of milk consumption on cardiovascular health is related to milk's saturated fat content (70% of total milk fat is saturated), resulting in increased blood lipids, especially cholesterol and low-density lipoproteins [22]. However, investigations on the link between dairy consumption and the risk of cardiovascular diseases (CVD) found that milk, cheese, and yogurt intake was inversely associated with CVD risk [23,24]. Several meta-analyses conducted on the relationship between milk intake and risk of CVD showed, in one study, a non-linear dose response relationship between milk intake and risk of stroke [25], while two studies [25,26] showed an inverse connection between cheese intake and stroke. However, the mechanism of the beneficial association of fermented dairy products and reduced CVD risk is uncertain. The reason for this uncertainty, at least in part, could be an effect of the food matrix reducing lipid absorption and short chain fatty acids produced by the bacteria in the large intestine [27]. Moreover, the beneficial effects of cheese can be accounted for by microbial fermentation producing short chain fatty acids such as butyrate [28]. Furthermore, the background, diet and lifestyle characteristics of study participants should be taken into account in the statistical analyses as major confounders [29]. Meta-analysis based on six

observational studies showed that low-fat, calcium-rich products were generally considered to decrease blood pressure, but there was no association of decreased blood pressure with intake of high-fat dairy products [30]. In accordance with newer meta-analyses, Nordic Nutrition Recommendations have concluded that high consumption of low-fat milk products is associated with reduced risk of hypertension and stroke [31].

Epidemiological and experimental studies have demonstrated that milk and dairy products can have preventive roles in the pathogenesis of colorectal, bladder, gastric, and breast cancer, but have no connections with pancreatic, ovarian or lung cancer [32]. On the contrary, a number of other epidemiological studies have reported an unfavorable effect of milk on prostate cancer risk [33,34,35]. However, experimental results are diverse and are further complicated by several factors, mostly because of the numerous bioactive components of milk, which can possibly interact with other components, including hormones and growth factors, but which remain unproven. Last, but not least, milk digestion and its metabolites must also be considered in order to understand the effect of dietary compounds on specific cells in the human body. Taken altogether, the complex composition of dairy food matrices and the heterogeneity of cancer as multiple diseases make this a challenging area of study.

Milk consumption is also related to lactose intolerance or allergies [36]. Although the most common treatment for lactose intolerance was milk elimination diets, recent studies showed that most individuals with lactose intolerance can tolerate up to 12 g of lactose (250 ml of milk), which would provide 30% of recommended daily calcium intake. In addition, yogurts prepared with *Lactobacillus delbrueckii* subsp. *bulgaricus* and/or *Streptococcus thermophilus* and hard, slow-ripened cheeses contain more predigested lactose and can be more easily tolerated than milk [37]. This is because bacterial lactase survives acidic conditions in the stomach, physically protected within bacterial cells and by the buffering capacity of yogurt. Furthermore, the slower gastrointestinal transit of these products than of milk allows the surviving bacterial lactase to be active and digest lactose [37].

Milk is not “just a food”. The growing body of evidence demonstrates that milk is a sophisticated materno-neonatal species-specific signaling system, activating one of the central and key nutrient-sensing pathways – the mammalian target of rapamycin complex 1 (mTORC1) [38]. The activation of the mTOR pathway promotes cell growth, cell division, lipid and nucleotide biosynthesis and gene expression; thus, it positively regulates anabolic processes. Branched-chain amino acids, especially leucine, are known as positive regulators of mTORC1 signaling. Notably, of all animal proteins, whey proteins contain the highest amount of leucine (14%) as compared to meat (8% leucine). As *Bos taurus* duplicates birth weight four times faster than *Homo sapiens*, it is understandable that bovine milk, in comparison to human milk, triggers a much higher magnitude of mTORC1 signaling. Recent evidence from molecular medicine supports the view that persistently increased mTORC1 signaling is regarded as the driving force of non-communicable diseases like hypertension, osteoporosis, obesity, type 2-diabetes, cancer and neurodegenerative disorders [39]. A deeper understanding of milk signaling functions are needed in order to get more insight into the overall life history consequences of milk in the human diet.

#### 4. Conclusion

Given that milk and dairy products have been important components of human diets for over 8000 years, it is conceivable that dairy farming practice could have created the selective pressure under which the LP allele was favored and persisted. Although the milk-derived bioactive peptides, with their physiological versatility, seem useful to target at diet-related chronic diseases, as yet, there has been limited scientific information in this field due to a lack of molecular studies. Overall, the proven health benefits of consuming milk and dairy products greatly outweigh the possible harmful effects. Long-term randomized controlled intervention studies are, however, required to give more conclusive answers on the health aspects of dairy products.

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