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Current Opinion in Food Science

Update on bioactive peptides after milk and cheese digestion

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Bioactive peptides represent an interesting alternative to pharmaceutical drugs without known side effects, as they are present in a variety of protein-rich foods that are consumed on a daily basis. Most of these peptides are embedded and inactive in their parental protein and must be cleaved during food-processing, bacterial fermentation, or gastrointestinal digestion. In recent years, bioactive peptides have attracted increasing interest in the research community, and many health-promoting effects have been attributed to specific amino acid sequences. This mini-review provides a summary of the most important biological functions that have been described for bioactive peptides in various review papers, and an update on findings from the last two years for specific milk- and cheese-derived bioactive peptides.

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Current Opinion in Food Science 2017, **14**:116–121

This review comes from a themed issue on **Functional foods and nutrition**

Edited by **Cristina Delgado-Andrade**

For a complete overview see the Issue and the Editorial

Available online 29th March 2017

http://dx.doi.org/10.1016/j.cofs.2017.03.003

Introduction

Milk products are not only a good source for proteins of high nutritional value but also for a multitude of bioactive peptides generated either by fermentation processes [1] during yogurt- or cheese-manufacturing or by gastrointestinal digestion after consumption [2,3]. The increasing number of publications that appeared during the last years, show that the interest in bioactive peptides in food is growing. Many studies have been performed to identify the peptides at different levels of protein degradation, including in the original products [4], after *in vitro* [5] or *in vivo* [6,2,3] digestion, after *in vitro* absorption through a differentiated cell layer [7–10], simulating the intestinal barrier, and after *in vivo* absorption in the serum of test animals [11] or human subjects [12••]. To attribute a specific function to a certain peptide, the peptides were incubated *in vitro* in cell culture models, ingested *in vivo*, or injected into the bloodstream. A limited number of studies have shown the presence of peptides in the serum; however, the main challenge of the current research is to show direct health benefits from these peptides in a pharmacological dose-dependent manner.

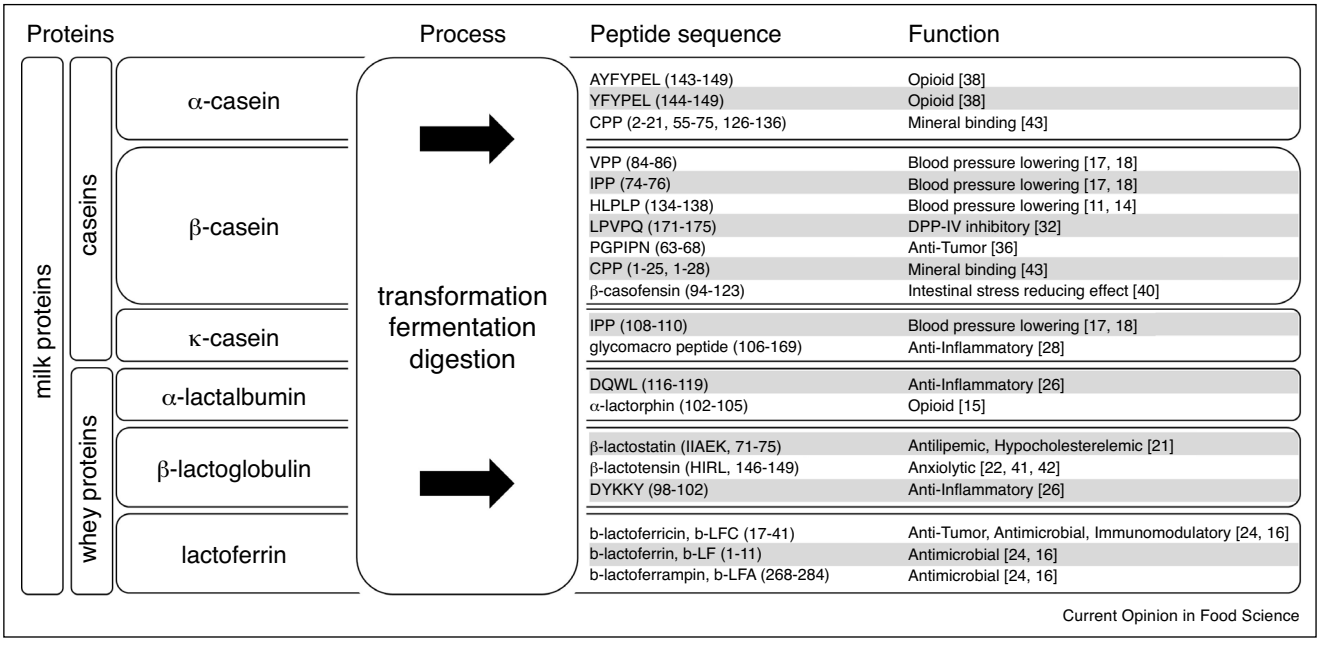
Literature search

The literature search for this review, using the keywords 'milk-derived bioactive peptides' and 'cheese-derived bioactive peptides'; restricted to the years 2015 and 2016; was performed on PubMed; Web of Science; and SCOPUS. The search yielded in a total of 139 documents; of which 56 documents were out of the review focus; 40 documents were review articles; and 44 were original publications. The original research articles from the year 2016 and selected review articles from 2015 to 2016 were considered for this review. Some older articles are cited to support the recent findings. Throughout the article; the terms milk and milk products are used for milk of bovine origin and milk or milk products from other species are indicated specifically.

Bioavailability of bioactive peptides

Bioactive peptides are already present in high abundance in many different protein-rich foods, in especially in milk products after technological transformation or fermentation processes and even more are generated during the digestive process. Transport mechanisms and the bioavailability of bioactive peptides are often studied with identified and isolated peptides or in cell culture models [13]. However, if and how many of the ingested peptides are absorbed and reach the blood *in vivo* is a subject of current research. A recent study by Caira *et al.* [12••] identified in a pilot human trial in which subjects ingested 100 g of Parmigiano Reggiano (1 g caseinophosph-peptides, CPPs) per day for one week, specific CPPs in the plasma. An animal study performed on spontaneous hypertensive rats (SHR) with an oral mono-dose of the antihypertensive pentapeptide HLPLP (β-casein) showed that 5.18% of the peptides were transported. The peptides had a short half-life in the plasma but induced a reduction in blood pressure (BP) in the treated animals [11,14••]. Besides bioavailability, oral tolerance to proteins or peptides is a critical point toward generation of new nutraceuticals as alternatives for pharmaceutical drugs. So far, the different literature resources reported that oral administration of isolated proteins or peptides was well tolerated and no side effects were observed

Figure 1



The main milk-derived bioactive peptide sequences described in this mini-review compiled from review or research from the years 2015 to 2016 with their *in vitro* or *in vivo* activities, the amino acid bioactive sequence according to the IUPAC code, and the corresponding references.

[15••,16]. However, this needs to be investigated for each case in a similar way as for bovine Lactoferrin (b-LF) which was approved by the US and European Food Safety authorities as dietary supplement [16].

Functions of bioactive peptides

Many different *in vitro* and *in vivo* functions of bioactive peptides have been described in the literature. This mini-review provides a brief summary of the most commonly investigated bioactivities described in the recent literature for milk-derived peptides. The specific amino acid sequences, their localization within the whole protein, and the corresponding references are summarized in Figure 1. For each topic, several recent review articles for in depth information and further reading are listed in Table 1.

BP-lowering effects

The best-studied and *in vivo*-confirmed effect of bioactive peptides is their BP-lowering function [17,18,15••,19••]. Different mechanisms of action for bioactive peptides are responsible for this phenomenon:

Table 1

Topics with selected reviews for further reading

Section	Bioactive effects	Reference
Bioavailability of bioactive peptides	Bioavailability	Nongonierma and FitzGerald [43], Boutrou *et al.* [3], Segura-Campos *et al.* [9]
Functions of bioactive peptides	General effects	Cicero *et al.* [15••], Marcone *et al.* [30]
BP-lowering effects	BP-Lowering	Aluko [17], Beltran-Barrientos *et al.* [18], Cicero *et al.* [15••],
Antilipemic effects	Antilipemic	Marcone *et al.* [30], Yoshikawa [21], Cicero *et al.* [15••]
Immunomodulatory effects	Immunomodulatory	Marcone *et al.* [30], Santiago *et al.* [23], Cicero *et al.* [15••]
Anti-inflammatory effects	Anti-inflammatory	Majumder *et al.* [44], Marcone *et al.* [30], Cicero *et al.* [15••]
Effects on glycemia	Glycemia	Horner *et al.* [29], Marcone *et al.* [30]
Insulinotropic effect	Insulinotropic	Marcone *et al.* [30]
Effects on satiety	Satiety	Nongonierma and FitzGerald [19••,43]
Anticancer effects	Anticancer	Blanco-Miguez *et al.* [33], Cicero *et al.* [15••], Zhang *et al.* [34]
Opioid effects	Opioid	Nongonierma and FitzGerald [19••]
Antimicrobial effects	Antimicrobial	Bruni *et al.* [24], Giansanti *et al.* [16], Mohanty *et al.* [45]
Diverse bioactivities	Antioxidant, mineral-binding, antithrombotic	Marcone *et al.* [30], Nongonierma and FitzGerald [19••], Giansanti *et al.* [16]