Health and nutritional aspects of cheese with a focus on bioactive peptides

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Institute of Food Science Research
Nutritional aspects of cheese

Adverse nutritional image
- Saturated fatty acids
- Cholesterol
- Salt
- Cardiovascular disease

Essential nutrients for a healthy diet
- Short chain fatty acids
- CLA
- Minerals: Ca, P
- Vitamins
- Proteins ⇒ Peptides

Not all saturated fats elevate plasma cholesterol to the same extent

Ash & Wilbey, Int J Dairy Technol, 2010
Cheese composition

Walther et al., Dairy Sci Technol, 2008

All types of cheese, except fresh cheese are practically lactose-free
Fat

- Cheese fat varies between 20-35% (w/w)
- In summer SFA are reduced in favor of MUFA and PUFA

Cheese fat composition (g/kg)

- Stearic; 80
- Others; 15
- Myristic; 98
- Palmitic; 260
- MUFA; 250
- PUFA; 46
- SFA; 600

- Individual SFA can affect blood cholesterol differently
  - Stearic acid (13% of SFA) is rapidly converted to oleic acid (C18:1) in the body
  - Fatty acids in cheese: ↑LDL cholesterol but also ↑HDL cholesterol

Beneficial cholesterol profile
(↑ Total HDL:cholesterol ratio)

- 100 mg dietary cholesterol slightly increase plasma cholesterol
Fat

Biological activity of cheese fat components

- **BUTYRIC ACID**: regulate gene expression ⇒ role in cancer prevention
- **CAPRYLIC AND CAPRIC ACID**: antiviral activity
- **PHOSPHOLIPIDS**: anticancer, immunomodulatory, neuronal cell functions
- **CLA**: cancer prevention, hypertension, atherosclerosis, diabetes, improve immune function and body composition

- Cheese fat supplies vitamins (A, D, E, K)

Walther et al., Dairy Sci Technol, 2008
Mills et al., Int. Dairy J, 2011
Ash & Wilbey, Int J Dairy Technol, 2010
**Minerals**

- Important source of Ca, P and Mg. High bioavailability.
- 100 g serving of hard cheese provides approx. 800 mg calcium
- Recommended daily intake calcium adults (19-50 yrs) = 1000 mg/day

<table>
<thead>
<tr>
<th>Food</th>
<th>mg calcium per serving</th>
<th>No. servings to reach daily intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk, low fat (244 g)</td>
<td>264</td>
<td>3.8</td>
</tr>
<tr>
<td>Cheese, Cheddar (66 g)</td>
<td>476</td>
<td>2</td>
</tr>
<tr>
<td>Cheese, skim Ricotta (124 g)</td>
<td>337</td>
<td>3</td>
</tr>
<tr>
<td>Broccoli, cooked (156 g)</td>
<td>62</td>
<td>16</td>
</tr>
<tr>
<td>Tomates, stewed (255 g)</td>
<td>87</td>
<td>11</td>
</tr>
</tbody>
</table>

*Greer et al., Pediatrics, 2006*
• Importance of dairy products on diet to achieve an adequate calcium intake in order to reduce risk of fractures and osteoporosis later in life (Greer et al., Pediatrics, 2006)

• Dietary calcium plays a role in the regulation of energy metabolism and obesity risk (Zemel, J Am Coll Nutr, 2005)

  High calcium diets attenuate body fat accumulation and weight gain during periods of over-consumption of an energy-dense diet

• Calcium can partly account for the observed inverse association between dairy consumption and the risk of hypertension (Zemel, J Am Coll Nutr, 2001)
Nutritional aspects of cheese

Percentage of nutrients respect to the recommended daily value per serving

- Cottage, soft (113 g)
- Goat, semihard (28 g)
- Cheddar (66 g)

% Daily value per serving

- Phosphorous
- Calcium
- Sodium
- Fat
- Protein
- Calories
Proteins

Food derived peptides share structural motifs with endogenous peptides that play a crucial role in many physiological processes in the organism:

- neurotransmitters
- hormones
- antibiotics
Formation of bioactive peptides

**In vitro**
- Food processing: fermentation, ripening
- Hydrolysis with food grade enzymes
- Recombinant DNA technology
- Chemical synthesis

**In vivo**
Gastrointestinal digestion

- LF ➔ Lfcin
- CN ➔ CPPs
- CN ➔ opioid
Bioavailability of bioactive peptides

• Locally: intestinal tract or via receptors in the gut

• Elsewhere in the organism: Absorption

Does this molecule reach the target organ? In which form?
Activities of bioactive peptides

CARDIOVASCULAR SYSTEM
- Antihypertensive
- Antioxidant
- Hypocholesterolemic
- Antithrombotic

DIGESTIVE SYSTEM
- Antiobesity
- Protectors of the gastrointestinal mucosa
- Mineral absorption

BODY DEFENSES
- Antimicrobial
- Antiviral
- Immunomodulatory
- Antiinflammatory
- Antitumorals

NERVOUS SYSTEM
- Relaxing
Antihypertensive peptides

Mechanisms of action

- ACE-inhibitory activity
- Vasodilator effects in aortic rings
- Antioxidant activity
- Opioid-mediated antihypertensive effects

In vitro

Angiotensin-I

Angiotensin-II

DRYYIHPF

potent vasopressor

ACE

ACE Inhibitors

Bradykinin

hypotensive activity

Bradykinin inactivation

In vivo

Identification of novel sequences in cheese

Search for previously identified antihypertensive peptides
Antihypertensive peptides

Identification of novel sequences in cheese

Minimum ripening time
Manchego cheese
2 months

Type 1 cheese 8 m
for identification of
active peptides

Gómez-Ruiz et al., Int Dairy J, 2002
Antihypertensive peptides
# Antihypertensive peptides

<table>
<thead>
<tr>
<th>Protein fragment</th>
<th>Sequence</th>
<th>Protein (µg/ml)</th>
<th>% ACE inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-CN f(95-101)</td>
<td>VPKVKET</td>
<td>13,52</td>
<td>79,57</td>
</tr>
<tr>
<td>α_{s2}-CN f(165-170)</td>
<td>LKKISQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-CN f(95-100)</td>
<td>VPKVKE</td>
<td>33,33</td>
<td>80,11</td>
</tr>
<tr>
<td>β-CN f(47-51)</td>
<td>DKIHP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_{s1}-CN f(58-61)</td>
<td>KQMK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_{s1}-CN f(102-108)</td>
<td>KKYNVPQ</td>
<td>62,95</td>
<td>75,91</td>
</tr>
<tr>
<td>α_{s1}-CN f(86-91)</td>
<td>VPSERY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_{s1}-CN f(117-119)</td>
<td>FPE</td>
<td>61,63</td>
<td>79,14</td>
</tr>
<tr>
<td>α_{s1}-CN f(85-91)</td>
<td>DVPSERY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-CN f(1-6)</td>
<td>REQEEL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_{s2}-CN f(202-204)</td>
<td>IPY</td>
<td>7,7</td>
<td>53,68</td>
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<tr>
<td>α_{s2}-CN f(176-179)</td>
<td>AWPQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>various casein</td>
<td>FP</td>
<td></td>
<td></td>
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<tr>
<td>α_{s2}-CN f(195-204)</td>
<td>TQPKTNAIPY</td>
<td>40,38</td>
<td>82,74</td>
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<tr>
<td>α_{s1}-CN f(85-93)</td>
<td>DVPSERYL</td>
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<tr>
<td>α_{s1}-CN f(86-92)</td>
<td>VPSERYL</td>
<td>62</td>
<td>94,19</td>
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<tr>
<td>α_{s1}-CN f(109-114)</td>
<td>LEIVPK</td>
<td></td>
<td></td>
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<tr>
<td>α_{s2}-CN f(205-208)</td>
<td>VRYL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-CN f(199-204)</td>
<td>VRGPFP</td>
<td>18,2</td>
<td>99,7</td>
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<tr>
<td>α_{s1}-CN f(24-30)</td>
<td>VVAPFPE</td>
<td>37,9</td>
<td>100</td>
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<tr>
<td>α_{s1}-CN f(102-109)</td>
<td>KKYNVQPL</td>
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<tr>
<td>β-CN f(197-204)</td>
<td>GPVRGPFP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gómez-Ruiz et al., Int Dairy J, 2002
### Antihypertensive peptides

#### IN VITRO ACTIVITY SYNTHETIC PEPTIDES

<table>
<thead>
<tr>
<th>Protein fragment</th>
<th>Sequence</th>
<th>IC$_{50}$ (mM)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_{s2}$-CN f(205-208)</td>
<td>VRYL</td>
<td>24.1</td>
</tr>
<tr>
<td>$\alpha_{s1}$-CN f(86-92)</td>
<td>VPSERYL</td>
<td>249.5</td>
</tr>
<tr>
<td>$\alpha_{s1}$-CN f(86-91)</td>
<td>VPSERY</td>
<td>706.1</td>
</tr>
<tr>
<td>$\alpha_{s1}$-CN f(102-109)</td>
<td>KKYNVPQL</td>
<td>77.1</td>
</tr>
<tr>
<td>$\alpha_{s1}$-CN f(102-108)</td>
<td>KKYNVPQ</td>
<td>716.9</td>
</tr>
<tr>
<td>$\alpha_{s2}$-CN f(202-204)</td>
<td>IPY</td>
<td>206.0</td>
</tr>
<tr>
<td>$\alpha_{s2}$-CN f(195-204)</td>
<td>TQPKTNAPIY</td>
<td>3745.9</td>
</tr>
<tr>
<td>various fragments</td>
<td>FP</td>
<td>1215.7</td>
</tr>
<tr>
<td>$\beta$-CN f(199-204)</td>
<td>VRGPF</td>
<td>592.0</td>
</tr>
<tr>
<td>$\beta$-CN f(198-203)</td>
<td>PVRGPF</td>
<td>2834.0</td>
</tr>
<tr>
<td>$\alpha_{s1}$-CN f(109-114)</td>
<td>LEIVPK</td>
<td>1275.4</td>
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</tbody>
</table>

\(^a\) IC$_{50}$ values are shown for α-s2-CN (205-208) and α-s1-CN (86-92, 86-91, 102-109, 102-108, 202-204, 195-204), with various protein fragments and β-CN (199-204, 198-203) and α-s1-CN (109-114).

#### ACUTE ADMINISTRATION SHR

![Graph showing the acute administration of SHR with various peptides and IC$_{50}$ values](image)

**Graph:**
- Water
- Captopril
- KKYNVPQL (10 mg/kg)
- VRYL (10 mg/kg)

**IC$_{50}$ values:**
- Captopril: 24.1 mM
- KKYNVPQL (10 mg/kg): 249.5 mM
- VRYL (10 mg/kg): 706.1 mM
- KKYNVPQ: 77.1 mM
- IPY: 206.0 mM
- TQPKTNAPIY: 3745.9 mM
- Various fragments: 1215.7 mM
- VRGPF: 592.0 mM
- PVRGPF: 2834.0 mM
- LEIVPK: 1275.4 mM

**Source:** Gómez-Ruiz et al., *Int Dairy J*, 2004
Antihypertensive peptides

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</tbody>
</table>

$^a$ IC$_{50}$ values are in mM.

Gómez-Ruiz et al., Int Dairy J, 2004

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**ACUTE ADMINISTRATION SHR**

![Graph showing the effect of various peptides on SBP over time](image-url)
Antihypertensive peptides

Gómez-Ruiz et al., J Chromatogr A, 2004
Antihypertensive peptides

N- […]-X-X-Pro

Chemical synthesis → MS → conformers

BOC → 1 isomer trans-Pro → 113.8 µM

FMOC → 3 isomers: 2 trans-Pro, 1 cis-Pro → 577.9 µM

Gómez-Ruiz et al., J Agric Food Chem, 2004
Antihypertensive peptides

Search for previously identified antihypertensive peptides

_Lb. helveticus_  
*Saccharomyces cerevisiae*  
_Nakamura et al., 1995_

Systolic blood pressure -3.73 mm Hg  
Diastolic blood pressure -1.97 mm Hg

_Lactobacillus helveticus LBK-16H_  
_Seppe et al., 2002 and 2003_

IC\textsubscript{50}

V PP 9 \(\mu\)M  
IPP 5 \(\mu\)M

Doses 2.6-5.6 mg/day IPP+VPP

_Cicero et al., J Human Hypertension, 2011_
Antihypertensive peptides

Search for previously identified antihypertensive peptides

Meyer et al., J Dairy Sci, 2009
Bütikofer et al., J Dairy Sci, 2008
Bütikofer et al., Int Dairy J, 2007

40-45g semi-hard or hard cheese similar doses than in fermented products with blood-pressure-lowering properties
Antihypertensive peptides

FERMENTED MILK

$\beta$-CN f(133-138)
LHLPLP ($IC_{50}$ 5.4 $\mu$M)

HLPLP ($IC_{50}$ 21.6 $\mu$M)
In vivo active form

CASEIN HYDROLYSATE (LOWPEPT®)

$\alpha_{s1}$-CN f(90-94) RYLGY
($IC_{50}$ 0.71 mM)

$\alpha_{s1}$-CN f(143-149) AYFYPEL
($IC_{50}$ 6.58 mM)

Muguerza et al., Int Dairy J, 2006
Quirós et al., Int Dairy J, 2007

Contreras et al., Int Dairy J, 2009
Antihypertensive peptides

Search for previously identified antihypertensive peptides

Cheeses subjected to a hydrolysis process that simulates GD

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Activity</th>
<th>Cheese</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLPLP</td>
<td>Antihypertensive</td>
<td>Manchego; Serena; Tetilla; Gamonedo, Idiazabal, Valdeón</td>
</tr>
<tr>
<td>AYFYPEL</td>
<td>Antihypertensive</td>
<td>Manchego; Valdeón</td>
</tr>
<tr>
<td>YPVEPF</td>
<td>Opioid</td>
<td>Manchego; Serena; Tetilla</td>
</tr>
<tr>
<td>KVLVPVQ</td>
<td>Antihypertensive</td>
<td>Iberian cheese</td>
</tr>
<tr>
<td>RPKHPIK</td>
<td>Antimicrobial</td>
<td>Iberian cheese</td>
</tr>
<tr>
<td>GPVRGPFPPII</td>
<td>Immunomodulatory</td>
<td>Iberian cheese</td>
</tr>
</tbody>
</table>

Recio et al., 2011
Phosphoproteins

Phosphorylated regions of caseins

\[ \text{-SerP-SerP-SerP-Glu-Glu-Ile-Val-Pro-Asn} \]

*Bind divalent cations: Ca, Fe, Mn, Cu, Se
  - increased bioavailability
  - anticariogenic activity

*CPPs are released in the gut and accumulate in the lower part of the small intestine (ileum) where mineral absorption takes place:

  - Mini pigs: \( \alpha_{s1} \)-CN f(66-74) SerP-SerP-SerP-Glu-Glu-Ile-Val-Pro-Asn
    \( \text{Meisel & Frister, 1988} \)
  - Humans: \( \beta \)-CN CPPs found in duodenum \( \text{Chabance et al., 1998} \)
Phosphopeptides

In vivo controversial results:

Food matrix

• CPPs improve Zn & Ca absorption from a rice-based cereal but not from a whole-grain cereal (Hansen et al, 1997a) 😞
• Zn & Ca absorption were not influenced by CPP addition in phytate-containing bread meals (Hansen et al., 1997b) 😞

Physiological status

• Ca absorption improved in osteoporotic women with low absorptive capacity (Heaney et al., 1994) 😊
• Randomized crossover study with adults (n = 15), no differences were found (Teucher et al., 2006) 😟

Ratio CPPs/Ca; Ratio Ca/Pi

• Isolated rat ileum: CPP/Ca ratio of 15 maximize paracellular transport (Erba et al, 2002)
• Absorption of Ca is higher as CPP-Ca than CaCl₂ in presence of Pi (Erba et al. 2001)

Scholz-Ahrens & Schrezenmeir, Br J Nutr, 2000; Phelan et al., Int Dairy J, 2009
# Phosphopeptides

- **Water soluble extracts:**
  - Grana Padano \((Sforza et al., 2003)\)
  - Emmental \((Gagnaire et al., 2001)\)
  - Comté \((Roudot-Algaron et al., 1994)\)
  - Herrgard \((Ardö et al., 2006)\)

- **CPPs enrichment:**
  - Grana Padano \((Ferranti et al., 1997)\)
  - IMAC-Fe (III) Herrgard, Parmigiano \((Lund & Ardö, 2004)\)
  - Beaufort \((Dupas et al, 2009)\)

- **Simulated digestion:**
  - Manchego \((Nieto et al., in preparation)\)
  - Valdeón \((Diezhandino et al., in preparation)\)

- **Transient intermediate components susceptible to further hydrolysis**
  - No CPPs in Parmigiano Reggiano > 12 months
  - Comté and Emmental: no CPPs derived from \(\alpha_{s1}-CN\)
  - Parmigiano and Grana Padano \(\leq 6\) months: different CPPs from \(\alpha_{s1}-CN\)

- **CPPs with cluster SerP-SerP-SerP are more resistant to hydrolysis**
  - Dephosphorylation preferably occurs on isolated SerP residues
  - Only dephosphorylated residues are further degraded
Phosphopeptides

Increase in $\beta$-CN f(16-22) 3P during Grana Padano ripening

Leu-Ser-P-Ser-P-Ser-P-Glu-Glu-Ser

Ferranti et al., J Dairy Res, 1997
Phosphopeptides

**Other activities**

- **ANTIOXIDANT PROPERTIES:** due to sequestering of metal prooxidants *(Kitts, 2005)*
- **IMMUNOSTIMULATORY ACTIVITY:** Effect of CPP preparations with different Ca content in IL-6 release from cultured intestinal cells *(Kitts & Nakamura, J Dairy Res, 2006)*

![Stained Int-407 cells for IL-6](image)

Preparation with higher CPPs and Ca concentrations produced a positive response at inducing IL-6 secretion

- **Effect on growth and differentiation of osteoblastic cells** *(Tulipano et al., 2010)*

Bioavailability?
Opioid peptides

- Interact with opioid receptors and exert agonistic or antagonistic activities
- The adult human intestine is not permeable to casomorphins ⇒ gastrointestinal tract
- Casomorphins have been detected in plasma of neonates

**EFFECTS**

Reproductive role in the pregnant and lactating woman:
- regulation of blood glucose levels
- control of mammary gland functions

Effects in the neonate:
- Control of gastrointestinal functions, antidiarheal effect
- Immunoreactive material in central nervous system ⇒ sleep-inducing effect

Adults:
- Prolong intestinal transit time ⇒ modulation absorption of aa and electrolytes

Teschemacher et al., Biopolymers, 1997
EFSA Scientific Report 231, 2009
Opioid peptides

- Determination of agonistic and antagonistic opioid peptides in cheese extracts (ELISA)
- Changes in the mobility of isolated rabbit ileum

Sienkiewicz-Szlapka et al., Int Dairy J, 2009
Opioid peptides

LEVELS OF β-CASOMORPHIN-7 IN DIGESTED CHEESES

- Talegio
- Grana Padano (25 m)
- Grana Padano (17 m)
- Grana Padano (10 m)
- Gouda
- Gorgonzola
- Fontina
- Cheddar
- Caprino
- Brie

mg/kg

De Noni et al., Food Chem, 2010
Opioid peptides

Other activities

- Endogenous opioid systems regulate the growth of cancer cells ⇒ anticarcinogenic
- Antagonistic opioid peptides may stimulate phagocytes
- Milk opioid peptides stimulate mucin secretion in intestinal cells
Other bioactive peptides in cheese

**Antiproliferative**

- Peptides from buffalo cheese whey have antiproliferative effect on stressed Caco-2 (de Simone et al., 2009; 2011)

F3 induces increased secretion of ceramides which resulted in cell cycle arrest, differentiation, “accelerated senescence” and cell death.

Opioid peptides?
Antioxidant peptides?

De Simone et al., *Mol Nutr Food Res*, 2011
Other bioactive peptides in cheese

Antiobesity

- Cheese diet attenuated the decrease in adiponectin from the adipose tissue after a calorie dense diet (Higurasi et al., Int Dairy J, 2007).

<table>
<thead>
<tr>
<th>Feeding period (weeks)</th>
<th>Adiponectin (µg mL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Control: 14.0, Cheese: 12.0</td>
</tr>
<tr>
<td>8</td>
<td>Control: 10.0, Cheese: 8.0</td>
</tr>
</tbody>
</table>

Production of adiponectin by addition of a Gouda derived peptide to primary cultures adipose cells

HPIKHQGLPQ $\alpha_{\text{s1}}$-CN f(4-13)

Concentration of serum adiponectin after a calorie-dense diet

- Ca from dairy prevents from obesity (Zemel, 2004)
- ACEI drugs increase adiponectin levels in humans (Philips & Kung, 2010)
Other bioactive peptides in cheese

Antiallergenic properties

• Peptide β-CN f(47-52) DKIHPF from Edam (other cheeses e.g. Manchego) inhibits β-Lg transport in an *in vitro* Caco-2 model (*Tanabe et al., J Dairy Sci, 2003*)

Antimicrobial peptides

• Caseins hydrolysed with proteinase *Lb. helveticus* PR4 ⇒ MIC 16 to 100 μg/ml (*Minervini et al., 2003*)

• Screening of chromatographic fractions of WSE Italian cheeses (*Rizzello et al., 2005*)

• Peptides from Australian Cheddar cheese showed activity against *Bacillus cereus* (*Pritchard et al., 2010*)
Antimicrobial peptides

MIC of several fractions isolated from Italian cheeses (Rizzello et al., J Dairy Sci, 2005).

- Yersinia enterocolitica
- Salmonella
- Staphylococcus aureus
- Listeria innocua
- Bacillus megaterium
- E. coli
- Lb helveticus
- Lb sakei A15

µg/ml

Caprino del Piemonte f19
Pecorino Romano f21

CSIC
Conclusions

NUTRITIONAL BENEFITS

- Low lactose content
- Calcium and phosphorous
- Proteins of high nutritional value
- SCFA, CLA phospholipids
- Vitamins (A, B₂, B₆, B₁₂)

BIOACTIVE PEPTIDES

- Phosphopeptides
- Antiproliferative
- Opioid
- Antihypertensive
- Antiobesity
Biopep Group

BIOPEP Group
Institute of Food Science Research
CIAL (CSIC-UAM)

COLABORATIONS:
Faculty of Medicine from University Complutense of Madrid-CSIC
Hospital Ramón y Cajal of Madrid
Faculty of Pharmacy from University of Salamanca
Faculty of Veterinary from University Computense of Madrid