POTENTIAL HEALTH IMPACT OF β-CASOMORPHINS AND RELATED PEPTIDES

Background
The primary structure of the polypeptide chains of ingested food proteins is enzymatically digested in the gastro-intestinal system to form smaller peptides and ultimately amino acids. The amount and type of intermediate peptides generated by the digestion of an original protein depend on the protein composition and the digestion conditions, like time, pH, and enzymatic activity. These latter parameters are in turn influenced by the individual’s age, genetic make-up, nutritional patterns and health state.

Some of the oligo-peptides (up to about 10 amino acids) may be biologically active; if they reach the intestine without further hydrolysis they may under particular conditions, like naturally permeable or leaky intestinal tract, pass into the blood stream intact. One class of such peptides has been shown to have the ability to mimic the effect of opiates in the brain. This property is shown, for example, by casomorphins, gluten exorphines, gliadorphin (gluteomorphin) and rubiscoisins (Table 1).

Table 1: Some of the known food derived opioid peptides.

<table>
<thead>
<tr>
<th>Dairy origin</th>
<th>Bovine β-casomorphin 1-4</th>
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</thead>
<tbody>
<tr>
<td>β-Casomorphin 1-3</td>
<td>* Structure: H-Tyr-Pro-Phe-OH</td>
</tr>
<tr>
<td>Bovine β-casomorphin 1-4, amide</td>
<td>* Structure: H-Tyr-Pro-Phe-Pro-NH₂</td>
</tr>
<tr>
<td>Bovine β-casomorphin 7</td>
<td>* Structure: H-Tyr-Pro-Phe-Pro-Gly-Pro-Ile-OH</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Cereal origin</th>
<th>Gluten exorphine A5</th>
</tr>
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<tbody>
<tr>
<td>Gluten exorphine A4</td>
<td>* Structure: H-Gly-Tyr-Pro-OH</td>
</tr>
<tr>
<td>Gluten exorphine B4</td>
<td>* Structure: H-Gly-Gly-Trp-OH</td>
</tr>
<tr>
<td>Gluten exorphine C</td>
<td>* Structure: H-Tyr-Pro-Ile-Ser-Leu-OH</td>
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<tr>
<th>Vegetable origin</th>
<th>Rubiscoin-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubiscoin-5</td>
<td>* Structure: H-Gly-Tyr-Pro-Thr-OH</td>
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</table>

Formation of the respective peptide depends on the amino acid sequence in the original protein. The amino acid sequence can vary slightly because of genetic polymorphism. Even small changes in the sequence can result in the possible release of a particular peptide during the digestion process. In the case of milk, for example, the genetically determined occurrence of different β-caseins results in different releases of casomorphins, β-casomorphin 7 (BCM-7) being one formed from the B β-casein or from the A1 β-casein, that differs only in one amino acid from the A2 β-casein.

Opioid activity is just one of many possible biological effects of peptides. The milk derived BCM-7 peptide as an example has been studied in detail and four different biological mechanisms suggested, apart from opioid activity they include lipid oxidation activity, histamine release and immunological reactivity.
The biological activity of such peptides, together with findings from some ecological studies\(^1\), raised in the last decades the hypothesis that BCM-7 or other bioactive peptides might be involved in the development of serious human diseases, like juvenile diabetes type I, ischemic heart disease, autism and schizophrenia.

Such hypotheses, if proven to be scientifically correct, would affect the consumption of extremely widespread commodities, therefore in the most recent years the scientific coverage of this subject has increased, partly with the support of interested parties. In some instances intellectual property has been filed, claiming genetic methodologies to select for the protein variants in order to reduce or eliminate the formation of the incriminated bioactive peptides during human digestion.

EFSA recognises the potential importance for human health of the issue of bioactive peptides from food digestion, should the alleged health effects be scientifically proven. Therefore EFSA deems it necessary to perform a comprehensive review of published information, to be able to assess the relevance and robustness of claims that BCM-7 and other related opioid peptides are associated with a wide range of non-communicable diseases.

**Terms of Reference**

Review the available evidence of the possible association, or lack thereof, between opioid peptides originating from food, such as BCM-7, and non-communicable diseases focusing on:

- Possible occurrence of BCM-7 or related peptides as a function of genetic variability of the food source;
- Factors leading to their formation, absorption in the intestinal tract and detailed metabolic pathways;
- Mechanisms of action of these peptides in the body, including immunological effects;
- A critical assessment of epidemiological evidence of adverse health effects in humans;
- A critical assessment of experimental evidence in animals fed with diets leading to high levels of BCM-7 or analogous peptides.
- Identification of possible specific vulnerability of particular sub-populations;

Following this review and depending on its outcome EFSA will decide whether there are sufficient indications to justify a full risk assessment of the consumption of food that can potentially produce such bioactive peptides during digestion. Should the review identify a lack of information on which to base a reasonable decision the need for any further research will be highlighted.

**Proposed Approach**

**Project steps**

A general brief outline of the project is the following:

1. Creation of working group / recruitment of experts
2. Collection of data, through:
   a. Bibliographic search

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\(^1\) Ecologic studies are different from epidemiological studies in the sense that they use data aggregated over groups rather than data on individuals. In these cases country level estimates on exposure were compared to country level disease data.
b. Voluntary contributions from interested parties

3. Organisation of data; proposed categories:
   a. Mechanisms of formation and absorption of peptides
   b. Mechanisms of action in the body
   c. Occurrence of protein precursors for the peptides
   d. Consumption
   e. Human epidemiological studies
   f. Animal trials

4. Evaluation and discussion of the scientific findings

5. Summary of data

6. Report preparation

**Expertise required**
- occurrence in relation to genetics of milk and vegetable proteins
- protein chemistry
- peptide biochemistry
- nutrition
- epidemiology and statistics
- medical expertise on specific diseases and the underlying physiology and biochemistry, including immunology

**PROPOSED TIMELINE**
An EFSA working group will be established during April 2008 to undertake the review. A first meeting is scheduled for 12 June 2008. The final report will be presented before the end of 2008.

**POTENTIAL FUNDING**
Some market research work might be necessary to clarify the range of products involved and other issues. This could be the subject of a grant agreement under Article36 or a procurement contract.