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1.4 How are Peptides Produced and Processed?

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1.4.1 Introduction

Peptides like proteins contain amino acid residues connected by peptides bonds that are considered as fairly stable under physiological conditions. Their sizes range from a few up to some 150 amino acid residues. Since there exists no clear cut definition for the term "peptide" to distinguish it from the term protein, we refer to peptides in a range from dipeptides to peptides with a molecular mass < 20 kDa, therefore small proteins may be included in our definition. The linear coding template for any peptide primary structure sequences is found in the genome. The origin of the word peptide is *peptein*, the Greek word for "to digest", or *pepsis* for digestion, introduced by the German chemist Emil Fischer (who has been awarded the Nobel Prize in chemistry in 1902), reminding us that peptides are usually generated by digestion (Fig. 4). This chapter will focus on the mechanisms that are responsible for the formation of peptides within higher organisms, and describe which factors – especially proteases – are determining peptide structure and peptide concentration.

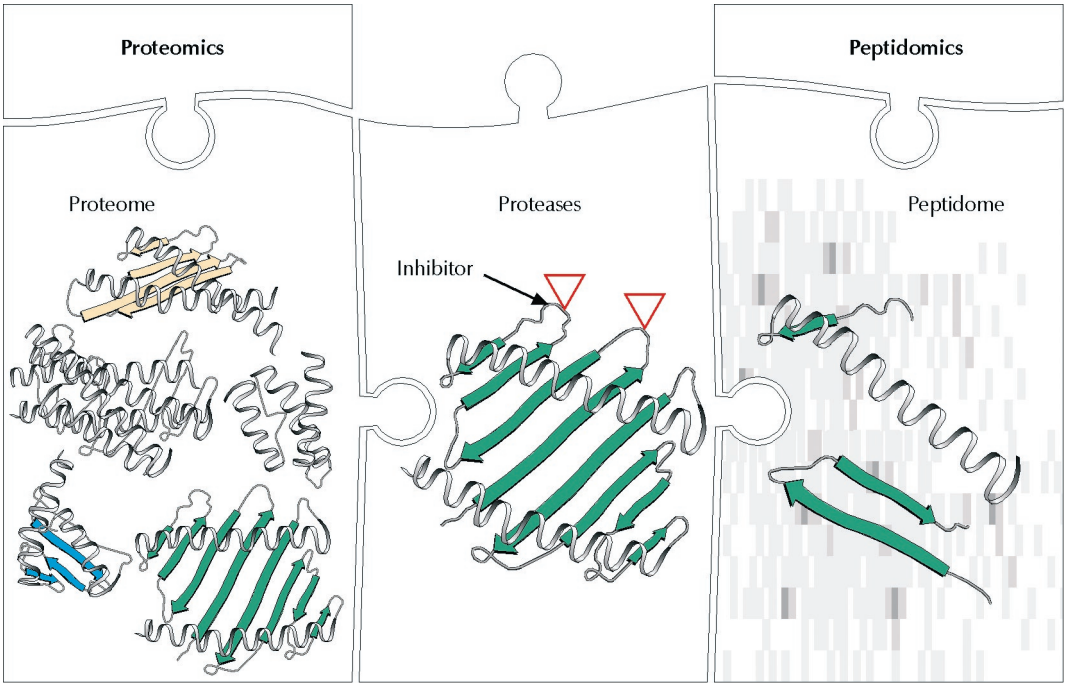

Fig. 4: Proteomics and peptidomics belong to post-genome technologies.
The proteome and the peptidome are complex settings that change with respect to location and time. Proteases and their inhibitors play a key role in the conversion of proteins to peptides, thus balancing proteome and peptidome.

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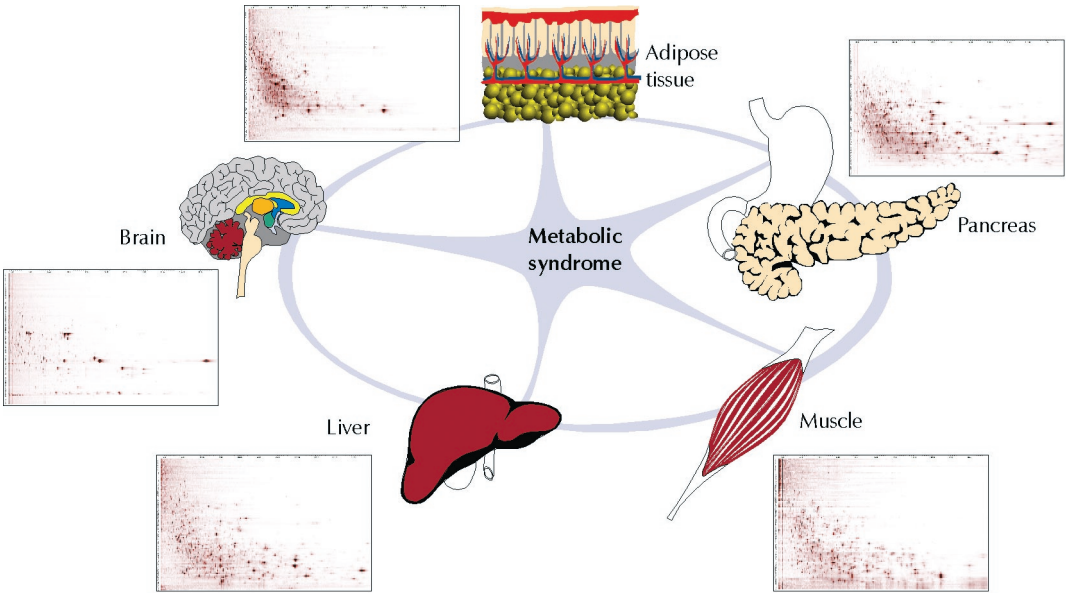

Fig. 46: Multi-organ involvement in metabolic syndrome.
Peptide displays of peptidomes from brain, skeletal muscle, liver, adipose tissue and pancreas from mouse. From sample amounts from 1 – 10 mg more than 1,500 endogenous peptides are displayed. All tissues have distinctly different peptide composition.

Mutation	Primary Defect	Phenotype	Application
Obese (lep^{ob}/lep^{ob} mouse)	Nonsense mutation in the adipose tissue derived hormone leptin prevents its inhibitory effect on food intake	Obesity, hyperphagia, transient hyperglycaemia, hyperinsulinaemia, insulin resistance	Preclinical model for obesity and insulin resistance
Diabetes ($lepr^{db}$/$lepr^{db}$ mouse)	Mutation in the leptin receptor gene causes defective leptin signalling	The clinical symptoms and course of the disease are more severe than in the ob/ob mouse	Preclinical model for type 2 diabetes
Fatty (Zucker fa/fa rat)	Leptin receptor	Obesity, insulin resistance, hyperinsulinaemia	Preclinical model for obesity and insulin resistance
Fat (cpe^{fat}/cpe^{fat} mouse)	A mutation in the carboxypeptidase E gene causes defective prohormone processing	Obesity, hyperglycaemia, insulin resistance, hyperinsulinaemia	Discovery of neuroendocrine peptides involved in the pathogenesis of obesity and insulin resistance

Table 5: Rodent obesity and type 2 diabetes models.

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3.4.2 Peptidomics in various areas of drug development

According to the judgment of the pharmaceutical R&D senior managers, peptidomics will play a significant role in drug development in all major fields of drug development within the next 5 years. The majority of the respondents predicted that the technology will impact medical diagnostics, prediction of therapeutic success, lead compound development, and molecular toxicology. Especially medical diagnostics was indicated by 96% of the respondents to be an important field of application. This may well reflect the physiological key role of peptides making them prone to be involved in pathological processes in a variety of medical indications. Also, diagnostics is frequently the first area in medicine to be infiltrated by novel technologies, peptidomics being obviously one example of this phenomenon. Consequently, only 4% of the respondents considered the potential impact of peptidomics on diagnostics as unpredictable, whereas for prediction of therapeutic success, development of lead compounds, and prediction of adverse events, the experts were less certain; 8%, 12% and 20% chose unpredictable in these areas, respectively. Especially for the comparatively novel area of molecular toxicology, the impact of peptidomics seems to be difficult to predict. However, this does not necessarily mean that peptides may not eventually increase in importance as molecular toxicology matures. There is increasing focus on toxicology markers particularly in the preclinical area and a recent review predicted that molecular toxicology will likely prove one of the most important applications of proteomics [112].

3.4.3 Peptide therapeutics

Although peptides have a high potential to be used as drugs, a drawback of peptide therapeutics is their rapid degradation after ingestion, and that is why they usually have to be administered by injection. However, currently the pharmaceutical industry is developing alternative intranasal, enteral, and inhalative administrations [113, 114]. This limitation may have caused 24% of the responders to predict that for the development of lead compounds, the importance of peptidomics is unlikely or very unlikely and 13% predicted that this field will not be important for peptidomics within the next 10 years. Compared to other compound classes peptide therapeutics tended to have a negative image in the industry in the past. Yet it often proved difficult to find adequate molecular substitutes – the most prominent example being insulin. Interestingly, our investigation shows that the majority of experts (64%) consider the importance of peptidomics in lead compound development as likely or very likely and 62% predict that the technology will become important in this field within the next 5 years. This clearly indicates that peptide therapeutics and/or peptidomimetic approaches for lead compound development are perceived much more favourably by the pharmaceutical industry than it may have been expected.

This change in view is also reflected by current pharmaceutical pipelines. In 2003 the global therapeutic peptide market amounted to 1 billion USD and currently more than 40 peptide based products are commercially available with 6 in the registration process. In Europe, about 4 to 6 peptide based products are in the market, with 100 in the clinical