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Review

Bioinformatics approaches, prospects and challenges of food bioactive peptide research

Chibuike C. Udenigwe*

Health and Bioproducts Research Laboratory, Department of Environmental Sciences, Faculty of Agriculture, Dalhousie University, Truro, Nova Scotia B2N 5E3, Canada (Tel.: +1 (902) 893 6625; fax: +1 (902) 893 1404; e-mail: cudenigwe@dal.ca)

There has been heightened effort to discover bioactive peptides from food and uncover their human health benefits based on preclinical evaluation systems. Consequently, a myriad of bioactive peptides are continuously reported with emerging interest in elucidating structure–function and molecular mechanisms. However, there is limited clinical evidence to substantiate bioactivity and minimal emphasis on translation into functional peptide products for health uses. This paper highlights the prospects of bioinformatics and a proposed integrated approach for enhancing the production of existing and new bioactive peptides from sustainable food protein sources, followed by discussion of the major challenges that may impact prospective commercialization of food bioactive peptides for use in human health promotion.

The many faces of bioactive peptides

Bioactive peptides discussed in this paper are comprised of two or more proteinogenic amino acid residues, joined together by peptide bonds, and are typically derived from enzymatic hydrolysis of proteins. These peptides are not active within the primary protein structure and must be cleaved intact to exert their functions; thus, the peptides can be referred to as "cryptic" meaning "hidden". The term "cryptide", a portmanteau for "cryptic" and "peptide", has also been used to describe bioactive peptides especially when encrypted within the parent proteins. Depending on proteolytic specificities, bioactive peptides can be released during processing and consumption of food proteins by gastric digestion, endogenous and exogenous proteolysis, and microbial enzyme action especially during fermentation (Beermann & Hartunga, 2013; Udenigwe & Aluko, 2012). The current trend in bioactive peptide research has been focused on their multifunctional bioactive properties that can be exploited for human health promotion (Fig. 1). Considering the current global health burden with metabolic disorders such as hypertension, hyperglycemia, hyperlipidemia, overweight and obesity playing leading roles as risk factors to mortality (World Health Organization, 2012), functional molecules derived from food have been widely pursued for mitigating these aberrations and restoring normal physiological functioning. Particularly, peptides have displayed beneficial effects that can be used for intervention against abnormal health conditions such as hypertension, hyperlipidemia, inflammation, diabetes, cancer, microbial infection, and immune disorder (Agyei & Danquah, 2012; Beermann & Hartunga, 2013; Udenigwe & Aluko, 2012). Based on the literature, the effects of bioactive peptides are typically exerted at the protein level mostly involving the inhibition of metabolic enzymes perhaps due to peptide–protein interactions that can perturb the structural conformation and enzymatic activities. Moreover, peptides can regulate the expression of genes responsible for abnormal signaling pathways but it is unclear if these activities are based on direct peptide–nucleic acid interactions or binding and inactivation of protein transcription factors that regulate such genes. Furthermore, peptides can also function by physical interaction and direct removal of metabolites leading to maintenance of physiological homeostasis, as demonstrated for hypolipidemic peptides that bind and excrete bile acids from the large intestine inhibiting their enterohepatic circulation and enhancing hepatic cholesterol metabolism (Howard & Udenigwe, 2013). The exact function of peptides depends substantially on their structures, which in turn depend on the nature of their protein precursor, liberating protease specificity and production conditions.

* Corresponding author.

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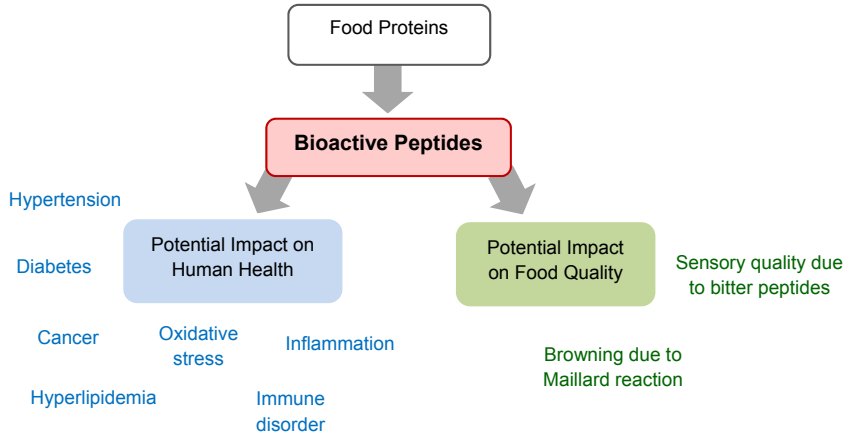

Fig. 1. The many faces of food bioactive peptides.

Therefore, it is important to define the structural requirements for bioactivity in order to develop efficient approaches for pursuing bioactive peptides particularly in selecting the parent proteins and enzymes for their liberation. Despite the prospects, the presence of peptides during thermal processing of food can potentially lead to undesirable attributes that may affect the quality, safety and consumer acceptability of finished products (Fig. 1).

Approaches for discovering bioactive peptides

A previous communication had suggested that the selection of food protein precursors of bioactive peptides is mostly based on the need to discover value-added use of protein-rich by-products of the agri-food industry, and exploit food proteins containing cryptic sequences with predetermined functions (Udenigwe & Aluko, 2012). In the present paper, considering the current literature, the major approaches in bioactive peptide research can be classified as illustrated in Fig. 2:

The classical approach

This represents the most widely used method for the discovery of bioactive peptides from food proteins, and typically involves selection of protein sources of particular interest to the researcher or industry. This is followed by protein hydrolysis with food-grade proteolytic enzymes of particular specificity, or those selected on the basis of previous studies that showed preference in liberating peptides of particular bioactivity, but not necessarily considering the unique interaction of the protease with the proteins. Subsequent fractionation and purification of the resulting protein hydrolysates with the appropriate matrix based on structural features of interest can result in purified peptides with particular bioactivity and prospective health benefit. Typically, the peptides do not proceed beyond this stage to commercial application. Often, the bioactive peptides are newly derived sequences and can be deposited in web-based open access databases of bioactive peptides such as BIOPEP (http://www.uwm.edu.pl/biochemia) and PepBank (http://pepbank.mgh.harvard.edu) for reference by the community of researchers. Recently, this approach was successfully used to isolate new bioactive peptides of pharmacological interest from food proteins (Ahn, Kim, & Je, 2014; He, Malomo, Girgih, Ju, & Aluko, 2013). The structures of the bioactive peptides can be used as templates for designing more active peptides and peptidomimetics, and for structure–function relationship studies. The major drawbacks of the classical approach include limited sample scope, time consumption especially during the purification steps, low yields of isolated peptides, and the likelihood that individually potent peptides may not be discovered after extensive processing typically when bioactivity is associated with additive or synergistic effects of various components of the enzymatic protein hydrolysates.

The bioinformatics approach

In order to circumvent some challenges of the classical approach, computer-based (often referred to as "*in silico*") simulation has been recently applied towards the discovery of bioactive peptides encrypted in food proteins (Carrasco-Castilla, Hernández-Álvarez, Jiménez-Martínez, Gutiérrez-López, & Dávila-Ortiz, 2012; Holton, Vijayakumar, & Khaldi, 2013; Lacroix & Li-Chan, 2012; Udenigwe, Gong, & Wu, 2013). With the advantage of simultaneously evaluating multiple food proteins and proteolytic enzymes, bioinformatics is well-positioned to make a transformative impact in bioactive peptide research. The *in silico* approach involves the use of information accrued in databases, such as BIOPEP (Dziuba, Minkiewicz, Nałęcz, & Iwaniak, 1999), to determine the occurrence frequency of cryptic bioactive peptides in the primary structure of food proteins. The protein sequences can be obtained from databases, notably the universal protein knowledgebase (UniProtKB)