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Review

Bioactive peptides derived from natural proteins with respect to diversity of their receptors and physiological effects

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ABSTRACT

We have found various bioactive peptides derived from animal and plant proteins, which interact with receptors for endogenous bioactive peptides such as opioids, neurotensin, complements C3a and C5a, oxytocin, and formyl peptides etc. Among them, rubiscolin, a δ opioid peptide derived from plant RuBisCO, showed memory-consolidating, anxiolytic-like, and food intake-modulating effects. Soymorphin, a μ opioid peptide derived from β-conglycinin showed anxiolytic-like, anorexigenic, hypoglycemic, and hypotriglyceridemic effects. β-Lactotensin derived from β-lactoglobulin, the first natural ligand for the NTS2 receptor, showed memory-consolidating, anxiolytic-like, and hypocholesterolemic effects. Weak agonist peptides for the complements C3a and C5a receptors were released from many proteins and exerted various central effects. Peptides showing anxiolytic-like antihypertensive and anti-alopecia effects via different types of receptors such as OT, FPR and AT_2 were also obtained. Based on these study, new functions and post-receptor mechanisms of receptor commom to endogenous and exogenous bioactive peptides have been clarified.

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1. Introduction

A concept that endogenous bioactive peptides are released by limited proteolysis of their specific precursor proteins was established in 1970s. As another route for the release of bioactive peptides, opioid peptides derived from casein and gluten, which has not been regarded as precursors of bioactive protein, were reported in 1979 [1,2]. The term exorphin was given for those opioid peptides of exogenous origin by Zioudou [2,3]. Since then, a lot of examples in which bioactive peptides are released from natural proteins have been reported. It should be noted that peptides acting on animals are released not only of animal but also of plant origin. They are classified as follows: (1) ligands for receptors [1–3], (2) inhibitors for enzymes [4], (3) peptides modulating transport [5], (4) anti-microbial peptides [6], (5) anti-oxidative peptides [7].

In this article, peptides interacting with receptors for endogenous bioactive peptides and inhibitory peptides for some enzymes derived from animal and plant proteins are reviewed. Then, central and peripheral effects of selected bioactive peptides we found will be described with special reference to their receptors and post-receptor mechanisms.

The affinities of those peptides for receptors are much smaller than those of endogenous ones since they have only a few homologous amino acid residues with endogenous ligands. However, they exhibited central and peripheral effects after oral administration, a route that renders most endogenous bioactive peptides ineffective. This situation is caused partly because some of them are more resistant against gastrointestinal proteases than exogenous ones as typically shown in opioid peptides derived from natural proteins.

2. Natural proteins as precursors of bioactive peptides

Various kinds of bioactive peptides have been isolated from enzymatic digests of natural proteins of animal and plant origin. In Tables 1A and 1B, those peptides are classified according to the receptors or enzymes they interact.

2.1. ANIMAL proteins

2.1.1. Milk proteins

2.1.1.1. β-casein. β-Casomorphin (β-CM-7: YPFPGPI) has been isolated from a commercial peptone as an opioid peptide in an