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Review

PACAP-related peptide (PRP)—Molecular evolution and potential functions

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ABSTRACT

PACAP-related peptide (PRP) and PACAP are structurally related peptides that are encoded in the same transcripts. In the past, it was believed that the mammalian PRPs are evolved from GHRHs in non-mammals. With the recent discovery of authentic GHRH and receptor genes in frog and fish, this review aims to (1) coin the name of all GHRH-like peptides in previous literature as PRPs and (2) provide the background for new research direction for PRP in vertebrates. As a goldfish receptor highly specific for PRP with distinct tissue distribution has previously been characterized, it is highly possible that PRP plays a physiological role in non-mammalian vertebrates and the function of PRP has somehow been lost in mammals as a consequence of the loss of its receptor in the genome. This information may provide clues to elucidate functions of PRP in the future.

Contents

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1. Introduction

In 1989, a novel peptide capable of stimulating cAMP production in the pituitary was isolated from ovine hypothalamus, and hence was designated pituitary adenylate cyclase-activating polypeptide (PACAP) [33]. Its high degree of resemblance to vasoactive inhibitory peptide (VIP) prompted ardent investigation of the peptide. In 1990, cDNAs encoding precursor proteins of PACAP were cloned from ovine hypothalamus, human testis [21] and rat brain [38]. Interestingly, these studies revealed that the precursor protein also encoded a 29 amino acid PACAP-related peptide (PRP) in exon 4, at a region immediately upstream of the 38 amino acid PACAP. Based on sequence comparisons, both PRP and PACAP were then classified to the secretin/glucagon superfamily [3,7].

Apart from PRP and PACAP, the superfamily contains brain–gut peptides including secretin, glucagon, glucagon-like peptides (GLP-1 and GLP-2), glucose-dependent insulinotropic polypeptide (GIP), growth hormone-releasing hormone (GHRH), peptide histidine methionine (PHM) or peptide histidine isoleucine (PHI) and VIP [5,48]. Amino acid sequence alignment of these peptides demonstrated high levels of sequence identity at their N-termini, which is the bioactive core of these peptides [48]. In addition, similarities in receptor structures and signaling pathways [15,48] also indicate that these peptides were originated from a common ancestral gene.

Despite continuous efforts, PRP was isolated only in mammalian species [18,34,35,38,39,57,59], and no specific receptors for PRP have ever been characterized. In the superfamily, PRP is the only peptide whose function has remained an enigma since its discovery more than a decade ago [30,41,54]. Previously, a model on the evolution of PRP, PACAP, and GHRH was proposed in accordance with their structures and genomic organizations [15,35,48]. It was hypothesized that the mammalian GHRHs were evolved from non-mammalian GHRH-like peptides. In this hypothesis, duplication of the GHRH-like/PACAP gene took place just before the divergence of mammals, giving rise to the PRP/PACAP gene, via modifications of the GHRH-like sequences, and the GHRH gene by changing the PACAP sequences to the C-peptide.

Our recent study, however, provided new information regarding the evolution of PRP in non-mammalian vertebrates [24] (Fig. 1). We showed that the GHRH-like peptides in non-mammals (fish and amphibian) are in fact counterparts of mammalian PRPs; while a ''real'' GHRH that is capable of stimulating growth hormone (GH) release is distinctly present in another precursor protein, and hence in another gene, as in mammalian species. This conceptual revolution of the identities of GHRH and PRP in non-mammalian vertebrates sways the plausibility of the model previously proposed [15,35,48]. For this reason, in this review, the structure, function and evolutionary perspectives of PRP is examined in an attempt to explore new research areas regarding the potentially functional PRP in both mammalian and non-mammalian species.

2. Structure of PRP—from protochordate to mammal

2.1. Peptide length and cleavage site

2.1.1. Protochordate

Two PACAP precursors were cloned from a protochordate *Chelyosoma productum* [29], and both of them contained a ''PRP-like'' 27 amino acid protein. One PACAP precursor contains three exons that encode a signal peptide, PRP-like peptide, and PACAP1-27; whereas the other precursor contains four exons, encoding an additional cryptic peptide upstream of PRP-like peptide. In contrast, the structural organization of PRP/PACAP precursor is conserved in vertebrates, from fish to mammals (Fig. 2).

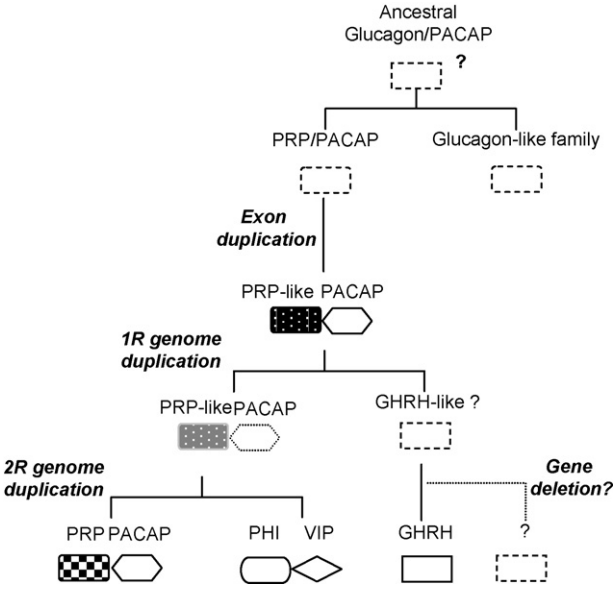

Fig. 1 – A proposed evolutionary model of GHRH, PRP–PACAP, and PHI–VIP genes with respect to two rounds of genome duplication [24]. Question marks denote uncertain events. Dashed line represents tentative genes.