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ScienceDirect
Regulatory Peptides 137 (2006) 95–104
REGULATORY PEPTIDES
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Review

Signaling mechanisms of secretin receptor

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Received 10 January 2006; received in revised form 14 February 2006; accepted 27 February 2006
Available online 22 August 2006

Abstract

Secretin, a 27-amino acid gastrointestinal peptide, was initially discovered based on its activities in stimulating pancreatic juice. In the past 20 years, secretin was demonstrated to exhibit pleiotropic functions in many different tissues and more importantly, its role as a neuropeptide was substantiated. To carry out its activities in the central nervous system and in peripheral organs, secretin interacts specifically with one known receptor. Secretin receptor, a member of guanine nucleotide-binding protein (G protein)-coupled receptor (GPCR) in the secretin/VIP/glucagon subfamily, possesses the characteristics of GPCR with seven conserved transmembrane domains, a relatively large amino-terminal extracellular domain and an intracellular carboxyl terminus. The structural features and signal transduction pathways of the secretin receptor in various tissues are reviewed in this article.
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Keywords: Secretin receptor; Signal transduction; Pathway; Structure; cAMP; IP_3

Contents

1. Introduction

Secretin carries out gastrointestinal [1–4] and neuronal functions [5] via its specific interactions with a cell surface receptor, the secretin receptor. Secretin receptor together with receptors

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0167-0115/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.regpep.2006.02.011

for other peptides in the same gene family including glucagon, glucagon-like peptides (GLP-1, GLP-2), glucose-dependent insulinotropic polypeptide (GIP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP) and growth hormone-releasing hormone (GRF or GHRH) [6], is grouped in the B1 subclass in the G protein-coupled receptor (GPCR) superfamily.

Rat secretin receptor cDNA was the first receptor cloned in the B1 subclass from rat/mouse hybrid NG108-15 cells by the expression cloning technique [7]. Later on, several identical human secretin receptor cDNAs were characterized from pancreatic adenocarcinoma cells and lung tissue [8–10]. The human secretin receptor contains 440 amino acids with a putative hydrophobic leader peptide (22 amino acids), a hydrophilic amino-terminal extracellular domain (122 amino acids), 7 transmembrane domains with 3 exo- and 3 endoloops (254 amino acids) and a carboxyl-terminal cytoplasmic tail (42 amino acids). It has been shown that the N-terminal extracellular domain and the first exoloop collectively constitute the ligand binding site [11–13]. The transmembrane domains that are highly conserved among members within the same family are involved in maintaining the structural conformation of the receptor in the lipid bilayer [14,15] while the third endoloop is responsible for G protein coupling and signal transduction [16].

Secretin receptor is highly expressed in both pancreatic acinar and ductal epithelial cells while in extremely low or undetectable levels within the islets and pancreatic vascular structures [17]. In liver, receptor transcripts are exclusively found in cholangiocytes [18]. In stomach, secretin receptor is present in the circular and longitudinal smooth muscle layers of the proximal nonglandular forestomach [19], on the fundic membranes [20], in the antral parts of the gastric mucosa [21] and on the vagal afferent fibers innervating the forestomach [22]. In the brain, expression of secretin receptor is high in the cerebellum, intermediate in the cortex, thalamus, striatum, hippocampus and hypothalamus while low in the midbrain, medulla, and pons [5,23,24]. Recent study by Nozaki S et al. demonstrated that secretin receptor is also expressed in the nucleus of the solitary tract (NTS), accumbens nucleus, lateral septal nucleus, olfactory bulb, amygdale, pineal gland, caudate/putamen, pituitary; and also in cingulate, piriform, frontal, parietal, entorhinal, and orbital cortices [25]. In reproductive system, secretin receptor transcripts and receptor-like signals were observed throughout the epithelium of caput and cauda epididymis [26]. Additionally, these signals have also been located on the smooth musculature of the intestine as well as in the colon [27]. Secretin receptor transcripts and specific binding sites were also shown in heart [7], lung [28] and outer medulla of the kidney [29], clearly indicating a wide spectrum of biological functions played by secretin.

The binding of secretin to its receptor triggers the activation of intracellular secondary messenger systems and hence various cellular processes [30]. Recently, it was shown that secretin could inhibit cell cycling and the binding of secretin with a dominant-negative receptor splice variant could lead to pancreatic carcinogenesis [31]. In summary, the understanding of the cellular mechanisms arising from secretin–receptor interaction is crucial to future investigation of the physiology and pathophysiology of secretin.

2. Ligand binding

By constructing chimeric secretin/VPAC1 receptors, the amino termini and the first exoloops of these receptors were found critical for ligand binding [11,12]. Within these domains, the first 10 amino acid residues as well as Lys173, Asp174, Arg166, His189 and Cys190 in the first extracellular loop were found important. In addition, Phe257, Leu258, Asn260 and Thr261 in the second extracellular domain also contributed to ligand interaction [13,32,33]. On the other hand, mutation of Cys11, Cys186, Cys193 or Cys263 to Serine residue in the rat secretin receptor resulted in a reduced affinity for secretin, suggesting that the disulphide linkages involving Cys11, Cys186, Cys193 and Cys263 played a role in maintaining the structural conformation of the receptor [34]. In addition, glycosylation of the high mannose-type carbohydrate side-chains of the receptor was found important for conformational integrity that led to ligand interactions; in the human secretin receptor-transfected CHO cells, addition of tunicamycin and castanospermine, inhibitors for adding the core and high mannose-type sugars resulted in defective receptor functions. By mutation studies coupled to binding and confocal analyses, Asn72 was found to be the functional N-linked glycosylation site as mutation of Asn to Leu did not affect presentation of the mutant to the cell surface but still led to defective binding to iodinated secretin [35].

3. Signal transduction pathways

It is known that all the members in the B1 family of GPCR are capable of initiating intracellular accumulation of cAMP by coupling to adenylate cyclase via the G_s protein (Fig. 1) [6,36]. It was previously believed that the cAMP pathway was the sole signaling mechanism that gave rise to amylase release from pancreatic acinar cells and secretin had no effect on Ca^{2+} mobilization [37]. However, at high concentrations of secretin, cAMP accumulation was found maximum while amylase release was only half-maximum and there was a transient increase in intracellular Ca^{2+} [38]. These observations suggested the presence of an alternative signaling pathway and it was later demonstrated that secretin could also stimulate inositol triphosphate (IP_3), intracellular calcium and diacylglycerol (DAG) pathways in pancreatic acinar cells (Fig. 1) [38–40]. The following is a detailed account of the signal transduction mechanisms and the functions of secretin in various tissues of our body.

3.1. The central nervous system

The secretin receptor cAMP signaling pathway in neuronal cells was first demonstrated in rat/mouse neuroblastoma–glioma hybrid NG108-15 cells [41]. Similar results were obtained in subsequent studies by stimulating either the hybrid cells directly or receptor-transfected CHO or COS cells

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