Peptidergic Receptors

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Peptides and Intercellular Communication

Neuropeptides are peptides involved in nervous system function. They are synthesized in cells in large precursor proteins, and generally several biologically active peptides are contained in the same precursor molecule. In the 1970s the hunt for new peptides was intense, and an ever-growing list could be compiled. Peptidergic signaling molecules are widely distributed throughout the central and peripheral nervous systems and in the peripheral organs. They may act in a neurocrine, paracrine, autocrine, or endocrine manner; the same peptides may participate in intercellular communications through different modalities. For instance, many peptides expressed in the enteric system belong to a class of agents known as brain–gut peptides, functioning both as neuropeptides and gut hormones.

Neuropeptides may be co-stored with other neuropeptides or, alternatively, may coexist with 'classical' neurotransmitters in different cellular compartments. Different combinations of transmitters and peptides are found in ganglionic cells of the autonomic nervous system. For instance, the sympathetic postganglionic input to the heart arises in a large part from the stellate ganglion; these neurons commonly contain neuropeptide Y (NPY) in addition to norepinephrine, similar to almost all sympathetic postganglionic neurons innervating the vasculature of the gut and hindlimbs. Other sympathetic postganglionic neurons in the stellate ganglion project to the sweat glands using acetylcholine as their major transmitter (instead of the expected norepinephrine), and also contain at least two other peptides, that is, calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide (VIP). In addition, many postganglionic parasympathetic neurons contain acetylcholine and VIP. Thus, while autonomic neurons are commonly referred to as cholinergic or adrenergic, they may also contain permutations of other neuropeptide transmitters including angiotensin II (Ang II), enkephalin, neurotensin, substance P (SP), somatostatin, CGRP, etc. Functionally, specific permutations of transmitters may comprise a 'chemical code' for neurons subserving specific actions. Co-stored peptides and classical transmitters are released together at all terminals of a given neuron, and they act together in determining the responses of target cells. It is a general rule that when a peptide and a classical transmitter coexist, the first mediates long-lasting responses and the latter short-term synaptic events in the target cells.

Peptidergic Receptors

Independent of the modality, peptides act through specific receptors which are generally located on the plasma membrane of target cells, although there is growing evidence that certain receptors are also present on the nuclear membrane. Peptidergic receptors belong to the superfamily of heterotrimeric G-protein-coupled receptors (GPCRs), which are characterized by the presence of seven transmembrane domains. The specialized feature of these receptors is to achieve information transfer via the binding of ligands to a recognition domain and allosterically transmit the presence of that ligand to an intracellular domain that leads to G-protein activation. The human genome may code for more than 5000 GPCRs. Less than 10% are known, of which those activated by peptides represent a large proportion. In particular, mammalian peptidergic receptors are grouped into two families of GPCRs: the rhodopsin-like family (the largest family of GPCRs, also called class A), which contains the majority of the known peptidergic receptors, and the secretin-like family (class B). The ligand peptides for the receptors in the secretin-like family are relatively large polypeptides (27–141-amino-acid residues), and seven of them – glucagon, glucagon-like peptides 1 and 2, gastric inhibitory polypeptide, VIP, pituitary adenylate cyclase-activating peptide (PACAP), and growth hormone-releasing hormone – are structurally related.

It has been generally assumed that peptides exert their actions on GPCRs, but there are some exceptions. For instance, FMRFamide (Phe-Met-Arg-Phe-NH_2) and related peptides typically exert their action through GPCRs. However, two ionotropic receptors for these peptides have recently been identified which may have functional roles in the central and the peripheral nervous systems. Another example is one of the neurotensin receptors, which is a single transmembrane domain protein that belongs to a recently identified family of sorting receptors.

Although there is at least one receptor cloned for almost all of the peptides discovered so far, it still remains to be elucidated how many receptors can be