COMMUNICATION BETWEEN CELLS IN DISPARATE PARTS OF THE BODY HAS LONG BEEN CONSIDERED A HORMONAL FUNCTION IN WHICH SPECIFIC GLANDS RESPOND TO AN APPROPRIATE SIGNAL BY SECRETING A HORMONE OR AN "ACTIVE" COMPONENT OF THE CELL TO THE EXTRACELLULAR DOMAIN. IN RECENT YEARS IT HAS BECOME APPARENT THAT THIS CLASSICAL PATHWAY OF COMMUNICATION INVOLVING TRANSPORT PROTEINS, RECEPTORS, SECOND MESSENGERS, AND INTRACELLULAR FACTORS IS MUCH MORE COMPLEX THAN HITHERTO THOUGHT. AN EVER INCREASING NUMBER OF BIOLOGICALLY ACTIVE COMPOUNDS, SOME UNIQUE AND OTHERS CO-STORED AND SECRETED WITH WELL-KNOWN HORMONAL ENTITIES, HAVE BEEN DETECTED IN THE LAST DECADE AND HAVE DEMONSTRATED PROFOUND BIOLOGICAL ACTIVITIES IN THE MODULATION OF ACTION AND THE CONTROL OF SECRETION OF NUMEROUS TRANSMITTERS, ESPECIALLY IN THE FIELD OF NEUROSECRETION. MANY OF THESE COMPOUNDS HAVE BEEN SHOWN TO BE RELATIVELY SMALL PEPTIDES 3-20 AMINO ACIDS LONG, YET THEY SEEM TO BE CAPABLE OF EXQUISITE CONTROL OVER A VARIETY OF PHYSIOLOGICAL FUNCTIONS (1).

SOME OF THESE PEPTIDES HAVE EXHIBITED PRIMARY SIGNAL TRANSMISSION, AND ALSO ACTED IN A HORMONE-TYPE MANNER ON TISSUES NOT IN THEIR IMMEDIATE VICINITY. MANY OF THE ACTIVE COMPOUNDS ARE NEUROPEPTIDES, AND ARE FOUND IN THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM, WHILE OTHERS ACT IN THE GUT, THE CARDIOVASCULAR SYSTEM, AND THE UROGENITAL AND RENAL AREAS.

SYNTHESIS AND STRUCTURE

SYNTHESIS OF THE BIOLOGICALLY ACTIVE COMPOUNDS IS CARRIED OUT BY TWO MAJOR PATHWAYS. THE FIRST INVOLVES DE NOVO SYNTHESIS FROM AMINO ACIDS, WHILE THE SECOND PATHWAY BEGINS WITH A RELATIVELY LARGE PRECURSOR MOLECULE DEGRADED IN A SERIES OF STEPS RESULTING IN THE FINAL FORMATION OF ONE OR
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multiple active compounds. Biosynthetic mechanism is usually observed in the formation of small oligopeptides, such as the dipeptide carnosine (ala-his) or the tripeptide glutathione (glu-cys-gly), and involves the action of synthetases found in most eukaryotic tissues. The latter pathway is a more general mechanism following the pattern observed in the synthesis and segregation of many secretory proteins. It is carried out by the initial formation of a pre-pro-protein which is cleaved, trimmed, modified, and ultimately stored in discrete secretory granules in the cytoplasm of the cell. Some precursors contain multiple copies of the same peptide (Pro-enkephalin A contains four copies of met-enkephalin), while others may contain several distinct regulatory peptides (POMC contains peptide sequences with opioid, melanotropic, and corticotropic activities). This diversity creates a number of peptide precursors serving as origins of "families" of active compounds not necessarily similar in structure or their biological activity. The process may become even more complex if the possibility that the same precursor may undergo different processing in different tissues is considered. For example, the peptide cholecystokinin exists in three forms, two found in the intestine (CCK - 39, CCK - 33), while the third (CCK-8) is found in the brain. Similarly, somatostatin (SST) exists in two forms, one found in the brain (SST-14), while the other, which is the N-terminal extended form, is found in both the brain and the gut. In contrast, the processing of the precursor pro-opio-melanocortin (POMC), mainly found in the hypothalamus, results in the formation of a number of peptides with completely different activities, namely ACTH, MSH (three forms), endorphins, and lipotropin. In the same manner a single precursor is the "parent" of the peptide arginine vasopressin (AVP), oxytocin (OXY), and neurophysin. It is interesting to note that molecules similar (or identical) to the peptides in mammals and with the same modulatory or transmitter activity may be found in many lower species, such as the crustaceans, amphibians, and others. This may be seen for compounds such as substance P, vasopressin, oxytocin, and others (2).

STORAGE AND SECRETION

Many, if not all, of the biologically active compounds are formed, processed and stored in discrete secretory granules, and co-stored with the "classical" hormones and neurotransmitters (3). This localization results in their secretion by exocytosis from the secretory granules to the extracellular domain, together with the co-stored messengers, on an all-or-none basis. The action of the peptides, however, is not dependent upon or complementary to the secreted "major" transmitter. In many cases the presence of the active peptide in the secreted material is extremely short-lived due to the presence of extracellular peptidases, and thus their function in many tissues is still obscure.
The key step in the secretory event is the elevation of intracellular calcium following the activation stimulus. This takes place via influx of extracellular calcium into the cell through specific calcium channels, or the release of intracellular stores due to a signal generated inside the cell. As a result of the presence of a high calcium concentration within the cell, the secretory granules fuse with the plasma membrane in a process whose details are under intense investigation but still not clear, and their contents are discharged from the cell to the extracellular space and further to the circulation. Other peptides, nonneuronal in origin, are also secreted from storage following a variety of signals. For example, atrial natriuretic peptide (ANP) is secreted from granular cells of the left atrium in response to increased atrial filling and stretching of the atrial muscle, as well as by increased intracellular sodium or elevated osmolality (4). This active peptide is by immunochemical determination also found in noncardiac tissues such as lung, kidney, brain, salivary glands, spinal cord and autonomic ganglia, as well as in the adrenal medulla. Other families of active peptides include various growth factors stored and secreted in a number of tissues for autocrine growth, and cytokines which are synthesized, stored and secreted in the immune system as part of the regulation of the biochemical cascade initiated by the immunological response to external insults.

FUNCTIONS

Concentrations of most neuropeptides are in the order of 1 to 1000 pmol/g, which is much lower than those of the conventional neurotransmitters (10 to 10000 nmol/g). This quantitative difference has led some investigators to question the role of these peptides as neurotransmitters. Some neuropeptides, such as substance P, fulfill many of the criteria required of a neurotransmitter, yet the time necessary for their action is relatively slow. However, slow-conducting fibers exist in neuronal pathways where putative neurotransmitters might be active. Some peptides, such as VIP, have been shown to actively cause the release of catecholamines from the adrenal medulla, thus enhancing its role as a neurotransmitter. These effects of bioactive peptides as neurotransmitters are only now being elucidated, especially with the very recent findings of discrete foci in the brain for a number of various peptides.

NEUROMODULATION

Neuromodulation seems to be the major function of bioactive peptides. This is due to novel and exciting evidence for their effect as potentiators or inhibitors of hormonal and neurochemical activities. A classical example

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of neuromodulatory role of peptides is substance P, which is capable of modulating nicotinic responses both by activation or inhibition, depending on its concentration (5). Substance P has also been shown to modulate the effect of adrenergic ligands via a second messenger activation of its receptor or by modulation of β-adrenergic sites, and to possibly have a physiological role in regulation of the immune response. While the mechanism of action of substance P is not clear as yet, this peptide seems to have a key regulatory function in a number of physiological events. Another important and better characterized modulator activity of bioactive peptides is the releasing and inhibitory effect of a few of these compounds on the hypothalamus and the pituitary. Corticotrophin releasing factor (CRF) is secreted from the hypothalamus and modulates ACTH secretion from pituitary cells. This action is both modulator- and hormone-like, since this effect of CRF is carried out at a site remote from its tissue of origin, yet it is a “directed” effect in that this tripeptide is transported from the hypothalamus to the pituitary via a specific neural pathway and is not released to the circulation as “classical” hormones. A unique regulatory role is played by peptides found in both the gut and the brain, such as CCK, Bombesin and VIP. They have profound effects on the stomach and the intestinal mucosa, decreasing gastric emptying, while enhancing intestinal absorption by affecting the brush border cell metabolism, the contraction and the expansion of intestinal smooth muscle cells, and having a vasoactive effect on the intestinal vasculature. At the same time these peptides, in a slightly altered form, have a substantial effect in the brain on the appetite center, perhaps directly as neurotransmitters.

The modulator effect of SST (somatostatin) is characterized by its inhibitory effects on the secretion of a number of gastrointestinal hormones and peptides (e.g. insulin and glucagon), as well as a modulatory effect on brain peptide secretion (e.g. inhibits growth hormone secretion), and has thus received the title of “inhibin”. Many other bioactive peptides have been shown by immunohistochemistry to be present in a variety of neuronal and nonneuronal tissues, and are postulated to have a modulatory function. Investigation of the mechanism of their action is very difficult because of their low concentration and extremely small size, which make their detection and dynamics of activity very difficult for accurate observation. New analytical techniques will be instrumental in following up this mode of action of biologically active peptides.

HORMONE-LIKE ACTIVITY

Bioactive peptides demonstrating hormone-like activity are mainly nonneuronal by nature. The best characterized of these compounds are angiotensin II (AT-II), atrial natriuretic factor (ANF), and endothelin (ET). All three are formed by breakdown of precursor proteins, and are involved
in the regulation of renal epithelial transport. AT-II and ET are potent vasoconstrictors and have been shown to be extremely effective in the control of sodium flux in the kidney. ANF, on the other hand, antagonizes the systemic pressor effects of AT-II and appears to be important in the compensatory response to volume expansion, increasing fluid transfer from the blood to the interstitial space (6). The major problem in the hormone-like activity of these small peptides is their extremely short half-life in the circulation due to the action of peptidases. Thus, although a relatively large amount of enkephalins is released at each discharge of catecholamines from adrenal medulla cells (where a very high concentration is found co-stored with the catecholamines), they have no known peripheral function, and it is very difficult to detect them in plasma.

CONCLUSION

Bioactive peptides have a mainly modulatory role in human physiology, both in neuronal and nonneuronal tissues, but also have distinct functions as neurotransmitters and as hormones.

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