Pituitary adenylate cyclase-activating polypeptide and adrenomedullary function

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PITUITARY ADENYLATE CYCLASE-activating polypeptide (PACAP) is an ancestral molecule for a superfamily of 11 hormones and hormone-like substances that have a secretin-containing core in common. These include PACAP, glucagon, glucagon-like peptide-1 and -2, growth hormone-releasing hormone, VIP, peptide histidine methionine, secretin, and glucose-dependent insulinotrophic polypeptide (see extensive reviews, Refs. 9, 10). PACAP comes in two variants: a full-length 38-amino acid peptide and a truncated 27-amino acid peptide that is equivalent to the NH2-terminal amino acids of PACAP-38. PACAP has been identified in many species, including humans, birds, and fish. It is found also in an ancient protochordate, the tunicate (sea squirt, Chelyosoma productum). PACAP is very well conserved across species; thus there is 96% nucleotide identity between human and tunicate PACAP cDNA, suggesting that there has been a high evolutionary pressure to conserve PACAP ever since protochordates and humans separated their evolutionary lines more than 700 million years ago. Despite this, the exact physiological role of PACAP is as yet unclear.

Several PACAP receptors are known. They belong to the G protein-coupled seven-transmembrane segment receptors. There are PACAP-specific receptors (PAC1-R), which comprise eight splice variants from a single gene. The PAC1-Rs bind PACAP-27 and PACAP-38 with some variation in affinity among the splice variants, whereas they bind VIP with 100- to 1,000-fold lower affinity than PACAP. In addition, PACAP binds to the VIP receptors VPAC1-R and VPAC2-R with the same affinity as VIP. Nearly all the receptors couple to cAMP generation via adenylate cyclase and probably also to the phospholipase C-inositol trisphosphate system. An interesting exception is the PAC1-R-TM4 splice variant, which activates L-type calcium channels (9, 10).

PACAP was originally isolated from the pituitary gland (8), but it has now been found in virtually every tissue in the body and it has been ascribed functions as a regulator of cell cycle and development, of smooth and cardiac muscle function, of the immune system, of bone metabolism, of endocrine/paracrine function, and of exocrine gland function. PACAP is an ubiquitously distributed neuropeptide in the central nervous system and in peripheral neurons, where it acts as a cotransmitter involved in circadian rhythms and sensory and autonomic function, as for example insulin secretion after glucose ingestion (1). PACAP-deficient mice die if raised in a cool environment because of a reduced ability to develop adaptive thermogenesis (heat formation in brown adipose tissue mediated by norepinephrine-induced uncoupling of cellular respiration from ATP formation; 4).

In the adrenal gland it has been suggested that PACAP is a cotransmitter with acetylcholine at the adrenomedullary synapse and that PACAP may help to couple epinephrine biosynthesis to secretion during metabolic stress (5). In the isolated perfused rat adrenal gland, infusion of PACAP increases adrenal catecholamine output and electrical stimulation leads to an increased catecholamine release, which is inhibited by PAC1-R blockade (2). The PACAP-induced catecholamine release was inhibited by blockade of L-type calcium channels (3). Furthermore, in vivo infusion of PACAP into anesthetized dogs leads to an increase in adrenal catecholamine output, which is inhibited by a PAC1 receptor antagonist (6). The study by Lamouche and Yamaguchi (7) in the present issue of *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* demonstrates in vivo, in anesthetized dogs, that exogenous PACAP facilitated adrenal catecholamine secretion during hypotension, thereby adding an important piece of information to the emerging picture of PACAP as a cotransmitter in the adrenal gland.

Furthermore, Lamouche and Yamaguchi (7) stimulated splanchnic nerve activity by hypotension induced by infusion of sodium nitroprusside in the dog. Their results show that exogenous PACAP facilitated adrenal catecholamine secretion during hypotension. Stimulation of splanchnic nerve activity by insulin-induced hypoglycemia stimulates catecholamine secretion and thereby gluconeogenesis in the liver, which counteracts...
The hypoglycemia. In PACAP-deficient mice this mechanism is blunted, and insulin-induced hypoglycemia is lethal (5). Thus, in rats, mice, and dogs, PACAP seems to be involved in facilitating and enhancing adrenal catecholamine secretion after a variety of physiological stimuli, thereby supporting an important role for this hormone in the adaptation to a stressful environment.

REFERENCES