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Corticotropin-Releasing Hormone, Family of

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Glossary

corticotropin-releasing hormone (CRH)-binding protein A secreted protein that binds CRH-like peptides with affinity that is equal to or higher than that for the CRH receptors.

G protein-linked receptor A polypeptide containing seven-transmembrane spanning domains. The ligand-binding domain is found on the extracellular side of the plasma membrane. These receptors influence the activity of intracellular second messenger systems by interacting with G proteins in the plasma membrane.

hypophysiotropin A hormone produced in the hypothalamus and transported to the anterior pituitary that modifies pituitary hormone secretion.

neurosecretion Release of neurohormones from modified nerve terminals directly into a vascular supply. Organs capable of neurosecretion are referred to as neurohemal organs.

prohormone Precursor polypeptide that is processed by proteolytic cleavage to biologically active peptides or hormones.

stress Physical or emotional strain or tension capable of disrupting homeostasis. Immediate endocrine responses to stress are characterized by increased plasma concentrations of glucocorticoids. Behavioral responses to stress include increased arousal, escape behavior, anxiety-like behavior, and decreased sexual behavior.

Corticotropin-releasing hormone [CRH; also referred to as corticotropin-releasing factor (CRF)] is a member of a family of related peptides in vertebrates that includes the fish urotensins-I, frog sauvagine, and the urocortin/stresscopin peptides. CRF was first named for its stimulatory effect on corticotropin [also known as adrenocorticotropic hormone (ACTH)] secretion from the anterior pituitary gland. ACTH is the primary pituitary regulator of adrenal glucocorticoid biosynthesis and secretion. Members of the CRH family of peptides play central roles in the regulation of neuroendocrine, autonomic, and behavioral responses to physical and emotional stress.

THE CRH FAMILY OF PEPTIDES

The chemical nature of the corticotropin-releasing factor activity present in the vertebrate hypothalamus remained elusive until 1981, when Wylie Vale and colleagues isolated a 41-amino acid (aa) peptide from porcine hypothalami that was capable of stimulating pituitary adrenocorticotropic hormone (ACTH) secretion. Concurrently, Karl Lederis and colleagues isolated a 41-aa peptide with sequence similarity to corticotropin-releasing hormone (CRH) from the caudal neurosecretory organ (the urophysis) of the teleost fish, the common sucker (*Catostomus commersoni*), that they named urotensin-I (UI) based on its tissue of origin (urophysis) and its vasopressive activity. Since the early 1980s, several other CRH-like peptides have been isolated and some of their diverse physiological roles have been elucidated.

The vertebrate CRH family of peptides is composed of at least two distinct paralogous lineages, designated the CRH lineage and the UI/urocortin (UCN) lineage. CRH molecules, which are 41 aa in length, have been isolated from the brains of fishes, an amphibian, and mammals. Additional CRH-like peptides represented by the paralogous UI/UCN lineage were first identified in fishes; these peptides share approximately 50% sequence similarity with the CRHs. UCN, a 40-aa peptide, was isolated from the brains of rodents and human and shown to have 53–63% sequence similarity with fish UIs. Subsequently, two other UCN-like peptides that are 38 aa in length were predicted based on cDNA sequences isolated in mammals. These UCN-like sequences isolated from human were given the names stresscopin (SCP) and stresscopin-related peptide (SRP). Similar sequences were simultaneously isolated from mouse and designated urocortin-II (UCN-II) and urocortin-III (UCN-III). The human SCP and mouse UCN-III are homologous, as are the human SRP and the mouse UCN-II. The UCN-II and UCN-III peptides and similar sequences from pufferfishes (*Fugu rubripes* and *Tetraodon nigroviridis*) may

represent a separate, closely related lineage of the CRH family.

p0020 A 40-aa peptide that appears to be related to the UI/UCN lineage is sauvagine (SV), which was isolated from the skin of the frog *Phyllomedusa sauvagei*. Because this peptide has only been isolated from one frog species, and other UI/UCN-like peptides have not been identified in amphibians, the precise phylogenetic relationship of SV to the UI/UCN lineage is uncertain.

p0025 All CRH-like peptides are initially synthesized as a larger prohormone that is cleaved by prohormone convertases at dibasic residues to form the mature peptide; mature CRH-like peptides range from 38 to 41 aa residues. The cryptic peptide (N-terminal region of the prohormone) is cosecreted with CRH but has no known biological function. It is hypothesized that the cryptic peptide of the prohormone plays a role in intracellular protein folding and perhaps targeting to the secretory pathway.

s0010 MECHANISMS OF ACTION OF CRH-LIKE PEPTIDES: CRH RECEPTORS AND BINDING PROTEIN

p0030 The actions of CRH are mediated by specific receptors expressed in target cells and localized to the plasma membrane. In mammals, a number of distinct CRH receptor isoforms deriving from two paralogous genes and one secreted binding protein (CRH-BP) have been identified. The receptors appear homologous, each being a seven-transmembrane domain G protein-linked receptor and each transducing extracellular signals by stimulating intracellular cAMP production. The receptors exhibit differential rank order affinities for CRH peptides and tissue-specific patterns of expression. The first CRH receptor isolated in mammals, designated $CRHR_1$, is a 415-aa protein and was originally thought to not discriminate among the CRH or UI/UCN lineages (i.e., it possessed high affinity for all). However, findings show that $CRHR_1$ exhibits very low affinity for SRP/UCN-II and no measurable affinity for SCP/UCN-III (these peptides are selectively bound by $CRHR_2$). $CRHR_1$ is expressed in the anterior and intermediate lobes of the pituitary and in numerous sites throughout the brain.

p0035 A second CRH receptor subtype, $CRHR_2$, shares 70% sequence similarity with $CRHR_1$. The $CRHR_2$ has two splicing variants in rodents and three splicing variants in humans (humans: $CRHR_{2\alpha}$, 411 aa; $CRHR_{2\beta}$, 431 aa; $CRHR_{2\gamma}$, 397 aa). The $CRHR_2$ proteins possess significantly higher affinity for UI/UCN-like peptides than for CRHs. Significantly, SRP/UCN-II and SCP/UCN-III are selectively bound by the $CRHR_2$ proteins. In rodents, $CRHR_{2\alpha}$ is expressed in the brain within the lateral septal nuclei and regions of the hypothalamus, whereas $CRHR_{2\beta}$ is expressed in peripheral tissues (e.g., lung, skeletal muscle, ovary, cardiac myocytes, and gastrointestinal tract). In humans, all three $CRHR_2$ splicing variants are expressed in the brain, but only CRH-$R_{2\alpha}$ is expressed in peripheral tissues.

p0040 Studies of transgenic mice that lack one of the two CRH receptor genes support the hypothesis that the molecules subserve different physiological functions. Compared with wild type, $CRHR_1$ knockout (ko) mice exhibit lower plasma corticosterone concentrations, blunted ACTH responses to stress, altered adrenal morphology, and decreased anxiety-like behavior. $CRHR_2$ ko mice show altered adaptation to stress, increased anxiety-like behavior, and impaired cardiovascular function. Further advances in our understanding of CRH receptor biology have been possible due to the development of selective, nonpeptide $CRHR_1$ antagonists. For example, several pyrolopyrimidine compounds (e.g., antalarmin) have been found to selectively block CRH binding to $CRHR_1$ in a noncompetitive manner; this compound does not affect binding to $CRHR_2$ or the binding of other ligands to other G protein-linked receptors. Work on peptide-based $CRHR_2$-specific antagonists shows that this receptor can also be specifically targeted using pharmacological approaches.

p0045 A secreted CRH-binding protein (CRH-BP) was first isolated from human blood plasma. The structure of this protein has been elucidated in several mammalian species and in the frog *Xenopus laevis*. The protein ranges from 321 to 324 aa and exhibits a high degree of sequence similarity among species. Biochemical evidence indicates the presence of a CRH-BP in the brains of representatives of each vertebrate class. It is hypothesized that the CRH-BP modulates the bioavailability of CRH-like peptides. The CRH-BPs that have been characterized bind CRH-like peptides with affinities that are equal to or higher than those for the CRH receptors. This and other findings have led to the hypothesis that the primary function of the CRH-BP is to neutralize CRH activity by binding the peptide and making it unavailable to bind to receptors. It is also possible that the CRH-BP could function in targeting the peptide for clearance. Alternatively, the CRHBP could function to maintain high levels of CRH in the blood or within tissues, thus facilitating the action of the peptide. The CRH-BP is expressed at different sites depending on the species

(i.e., brain, liver, pituitary, intestine, and placenta), but all species studied express the protein in the pituitary and brain. Placental expression of the CRH-BP in humans has been implicated in regulating CRH bioavailability during late gestation; CRH is thought to play a critical role in the timing of parturition in mammals. Finally, studies of transgenic mice that either overexpress the CRH-BP or lack the CRH-BP gene indicate an important role for this binding protein in modulating CRH bioavailability.

EXPRESSION AND PHYSIOLOGICAL ACTIONS OF CRH-LIKE PEPTIDES

The expression of vertebrate CRH-like peptides in various brain regions and in peripheral tissues is consistent with their primary role in physiological and behavioral responses to stress. The synthesis and release of CRH increases in response to stress, and the peptide is implicated in the rapid increase in glucocorticoid biosynthesis by the adrenal glands, suppression of feeding, suppression of immune function, and enhanced locomotion, among others. The expression of CRH in neurosecretory neurons in the hypothalamus and the stimulatory action of CRH on pituitary ACTH secretion are common to all vertebrates. CRH is synthesized in hypothalamic nuclei (parvocellular neurons of the paraventricular nucleus in mammals) and is released at modified nerve terminals in the median eminence into the pituitary portal circulation. CRH is transported to the anterior pituitary gland, where it binds to its receptors and controls the secretion of pituitary hormones. CRH is also a potent releasing factor for thyroid-stimulating hormone in nonmammalian species. This thyroid stimulatory role for CRH has been implicated in the control of amphibian metamorphosis, which is a thyroid-dependent process. CRH also regulates α-melanocyte-stimulating hormone secretion in lower vertebrates, thus playing a role in skin pigmentary changes associated with background adaptation.

CRH-like peptides are expressed in brain regions outside of the neurosecretory cells of the hypothalamus, including the cortex, limbic system, and brainstem nuclei that are associated with autonomic function. Although there are differences in expression patterns among species, the basic brain region-specific patterns of expression are conserved among vertebrates. Prominent expression of CRH in mammals is observed in the cerebral cortex, tegmentum, amygdala/hippocampus (important for stress adaptation), brainstem (locus coeruleus), and spinal cord. Peripheral sites of CRH expression include the gut, spleen, thymus, skin, adrenal gland, and placenta. Expression of UCN tends to be more restricted than that of CRH, being found in the Edinger–Westphal nucleus of the tegmentum, the hypothalamus, and a small group of neurons in the telencephalon. Mouse UCN-II is expressed in stress-related cell groups in the hypothalamus and brainstem, and UCN-III is expressed in the hypothalamus and the medial amygdala.

The expression of CRH-like peptides in extrahypothalamic neural circuits has been implicated in their behavioral effects, where they are thought to function as neurotransmitters/neuromodulators, thus integrating behavioral and physiological responses to stress. In mammals, the actions of CRH peptides, in addition to their hypophysiotropic role, include control of appetite (to decrease food intake), behavioral responses to stress (arousal, escape, anxiety-like behavior, and diminished sexual behavior), enhancement of learning, alterations in cardiovascular function, and modulation of immune responses. Thus, in addition to their central role in the endocrine stress response through activation of the hypothalamic–pituitary–adrenal axis, CRH-like peptides also serve to integrate the autonomic and behavioral responses to stress via their actions in the central nervous system. CRH-like peptides are potent anxiogenic and anorectic agents, and their aberrant expression has been implicated in depressive, anxiety-related, and eating disorders.

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Further Reading

Challis, J. R. G., and Smith, S. K. (2001). Fetal endocrine signals and preterm labor. *Biol. Neonate* **79,** 163–167.

Dautzenberg, F. M., and Hauger, R. L. (2002). The CRF peptide family and their receptors: Yet more partners discovered. *Trends Pharmacol. Sci.* **23,** 71–77.

Denver, R. J. (1999). Evolution of the corticotropin-releasing hormone signaling system and its role in stress-induced phenotypic plasticity. *Neuropeptides Structure Function Biol. Behav.* **897,** 46–53.

Lovejoy, D. A., and Balment, R. J. (1999). Evolution and physiology of the corticotropin-releasing factor (CRF) family of neuropeptides in vertebrates. *Gen. Comp. Endocrinol.* **115,** 1–22.

Seasholtz, A. F., Burrows, H. L., Karolyi, I. J., and Camper, S. A. (2001). Mouse models of altered CRH-binding protein expression. *Peptides* **22,** 743–751.

Seasholtz, A. F., Valverde, R. A., and Denver, R. J. (2002). Corticotropin-releasing hormone-binding protein (CRH-BP): From fishes to mammals. Submitted for publication.

Speert, D. B., and Seasholtz, A. F. (2001). Corticotropin-releasing hormone receptors and ligands in stress: Who's on first? *Curr. Opin. Endocrinol. Diabetes* **8,** 161–165.

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