Review article

Expression and Role of Corticotropin-Releasing Hormone System in Malignant Cancers

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Abstract

Since the discovery of corticotropin-releasing hormone (abbreviated as CRF or CRH), the CRH peptide family has been extended to its receptors, namely CRF-R1/CRF1 and CRF-R2/CRF2, and to the newly identified peptides urocortin (UCN) I, II, and III. CRH and UCN I exert their effects via both CRF1 and CRF2, while UCN II and III exert their effects via CRF2 only. The downstream messengers of CRH and UCNs include cyclic adenosine monophosphate and extracellularly regulated kinase1/2. CRH is well known as a key endocrine factor of the hypothalamus-pituitary-adrenal axis while UCNs are known as peripheral stress adaptation agents, such as to heat, in normal tissues, such as the gastrointestinal tract and endometrial cells. Recently, several studies have reported that UCNs and CRH receptors are expressed in malignant cancers; however, the roles of CRH and UCNs in cancer physiology are under discussion. Recent studies have also reported that UCN I and its related peptides have potentially beneficial actions in cancer therapeutics, indicating that the derivatives of these peptides may be useful as anti-cancer agents or agents for adjuvant chemotherapy. In addition, while we previously reported on the intracellular transport of UCN I in glioblastoma cells, UCN I may also be transported to the cellular nucleus in renal cell carcinoma. Several studies revealed that CRF and UCNs exert inhibitory actions on cancer cells by mechanisms that may lead to potential use for cancer therapy. This review will describe the roles of UCNs and its related peptides in relation to cancer physiology and discuss the clinical perspectives of these agents in cancer therapy.

Keywords: CRH; urocortin; CRF receptors; cancer

Introduction

Corticotropin-releasing hormone (CRH) was identified in 1981 as a critical initiator of the stress adaptation system (i.e., the hypothalamic-pituitary-adrenal axis) [1]. Thereafter, the related peptides, such as its receptors, i.e., CRF type 1 (CRF-R1 or CRF1), type 2 (CRF-R2 or CRF2), and type 3 (CRF-R3) [2-5] receptors, and urocortin (UCN) I, II (or stresscopin-related peptide), and III (or stresscopin) were also identified [6-9]. CRH is well known as an endocrine agent in the hypothalamic-pituitary-adrenal axis while UCNs are known as locally active peptides that work as peripherally activated

anti-stress agents or neurotransmitter/neuropeptides in the central nervous system rather than as endocrine agents [10-12]. CRF1 consists of many types of variants that are generated by alternative splicing of the CRF1 gene and the structures of these variants result in various actions by CRF and related peptides, including the activation of various intracellular signaling mediators, such as cyclic adenosine monophosphate (cAMP) and nuclear factor- κ B, and the induction of serotonin release [13-15]. Recently, nine isoforms of CRF1 (CRF1a to CRF1i) have been reported [15]. In contrast, four isoforms of CRF2 (CRF2 α ,

CRF2 β , CRF2 γ , and a stomach isoform of CRF2) have been identified [4, 16-19]. These receptors have a common transmembrane structure with various extracellular structures. Therefore, these receptors may exert the same function (e.g., increasing intracellular cAMP, extracellularly regulated kinase [ERK] 1/2, etc.) but may have different affinities for their ligands [4, 20-22]. CRF-R3, which has a structure similar to CRF1, has been identified only in catfish, not in humans [5]. Based on these characteristics of the CRH receptors, the cellular effects of the ligands via expressed CRH receptors are varied. Therefore, some effects of CRH receptor ligands may be potentially involved in the protective actions of normal tissues and cells or in the cytotoxic effects of cancer cells. We will review the relations of CRH, UCNs, and their receptors in cancer physiology and discuss the possible applications of UCNs in cancer therapy.

Distribution of UCNs and CRF receptors in normal tissue

UCNs are ligands of the CRF receptors with UCN I being an agonist of CRF1 and CRF2 and UCN II and III being specific agonists of CRF2 [6-9]. CRF1 is expressed in the brain-including the anterior lobe of the pituitary from where adrenocorticotrophic hormone (ACTH) is released-skin, aortic endothelial cells, gastrointestinal tract, hepatocytes, pancreatic beta cells, mast cells, and myometrium. CRF2 is expressed in the brain, aortic smooth muscle cells, vascular endothelial cells (human aortic endothelial cells and human umbilical vein endothelial cells [HUVECs]), heart (including cardiac myocytes), skeletal muscle, gastrointestinal tract, hepatocytes, pancreatic beta cells, and myometrium, of which variants are mostly CRF2 α or CRF2 β . CRF2 γ is expressed only in the septum and hippocampus of the human brain [4, 23].

CRH and UCN I-III are ligands of the CRH receptors. CRH is mainly distributed in the central nervous system but is also expressed in the skin. UCN I is ubiquitously distributed in the central nervous system, pituitary gland, and normal peripheral tissues such as the skin, as well as the thyroid gland, heart, aortic endothelial cells and HUVECs, stomach, liver, gastrointestinal tract, colon, kidney, adrenal glands, lymph organs, gallbladder, prostate, testis, uterus, placenta, and myometrium, among others [23-26]. UCN I exerts its actions via CRF1 and CRF2, as well as CRH [6]. UCN II and III, which are considered to be specific ligands of CRF2 [7-9], are distributed in the central nervous system, heart, endothelial cells, adrenal glands, pancreas, placenta, granulosa lutein cells, gastrointestinal tract, and so on [7-9, 22, 25, 27-34]. UCN II is abundantly expressed in the brain, heart, adrenal glands, and peripheral blood cells while UCN III is expressed in the colon, small intestine, muscle, stomach, thyroid, adrenal glands, and pancreas [7, 8].

Expression of CRH receptors and its ligands in cancer cells

CRF1 is reportedly expressed in normal tissues and human tumor tissues, such as human brain glioblastomas, medulloblastomas, paragangliomas, neuroblastomas, some meningiomas, ACTH- and prolactin-producing pituitary adenomas, breast cancer, hepatocellular carcinoma (HCC), insulinomas, glucagonomas, endometrial cancer, ovarian cancer, melanoma cells, pheochromocytomas, adrenocortical adenomas, and human malignant melanoma (HMM) type II cells, as well as mouse pituitary gonadotropic L β T2 tumor cells, etc. [25, 35-44]. However, CRF1 is not detected in growth hormone (GH)- and thyroid stimulating hormone (TSH)-producing and non-functioning (gonadotropin-producing and null cell) pituitary adenomas, ependymomas, Ewing sarcoma, non-small lung cancer, exocrine ductal pancreatic carcinomas, gastrinomas, prostate cancer, and colon cancer [37]. CRF2 expression has been reported in prolactin-, GH-, and TSH-producing and non-functioning pituitary adenomas, mouse pituitary gonadotropic L β T2 tumor cells, glioblastomas, paraganglioma, breast cancer, gastric cancer, colorectal cancer (CRC), and endometrial and ovarian cancers [37, 41, 42, 44-47]. Our recent data revealed that A172 human glioblastoma cells express five isoforms of CRF1 (i.e., CRF1a, CRF1d, CRF1g, CRF1h, and CRF1i-b) and also CRF2 α [48].

CRH is sometimes pathologically expressed in cancer cells. CRH overexpression has been reported in human lung cancer cells-leading to ectopic Cushing's syndrome-in pheochromocytoma of multiple endocrine neoplasia type II, and in GH-producing pituitary adenomas [38, 49, 50]. In addition, CRH mRNA and/or protein have been detected in the glioblastoma cell lines KSN42, T98G, RT2, 9L, A172, and U-138 MG, as well as in pituitary cancer, Ewing's sarcoma, thyroid cancers (medullary, follicular, Hurtle, and insular), small cell lung cancer, pulmonary adenocarcinomas, gastric adenocarcinomas, pancreatic cancer, colon cancer (rectum and sigmoid), breast cancer, clear cell renal cell carcinoma, NCI-H295R human adrenal carcinoma cells, endometrial cancer, and ovarian cancer [23, 41, 42]. UCN I, II, and III are also expressed in various cancer cell lines, including the human glioblastoma cell lines KSN42, T98G, RT2, 9L, A172, and U-138 MG, pituitary adenomas, malignant melanoma cells, both thyroid carcinoma and pheochromocytoma (multiple endocrine neoplasia type II), breast cancer, the gastric adenocarcinoma cell line STKM-1, colon cancer, primary and metastatic liver carcinoma, pancreatic ductal adenocarcinoma, neoplasms, the insulinoma cell line MIN6, clear cell renal carcinoma, adrenal tumor and NCI-H295R human adrenal carcinoma cells, human endometrial carcinoma, human prostate adenocarcinoma, and melanoma cells, among others [23, 25, 43, 47, 50, 51]. In some cancer cells, endogenous UCNs and related peptides are downregulated [36, 47, 52, 53]. Interestingly, UCN I may be transported via the constitutive pathway in human glioblastoma cells [46]. Tezval et al. [51] reported that UCN I-like immunoreactivity was

detected in the nucleus of human renal cell carcinoma. The details on an intracellular transport mechanism of UCN I still need to be clarified.

Although CRH, UCNs, and their receptors are not always co-localized in the same cell [23], the distribution of CRF receptors implies that an agonist or antagonist of the CRF receptors may have a potential pharmacological role in the efficacy of cancer therapy.

Clinical perspectives of CRF-related peptides in cancer treatment

It has been reported that UCNs stimulate several signaling molecules, such as cAMP and ERK1/2, p38 mitogen-activated protein kinase, and c-jun N-terminal 1/2, etc., via CRF1 and CRF2 [20-22, 54, 55]. Recently, Lawrence et al. [56] showed that blocking CRF1 resulted in the upregulation of p53, a potential suppressor of cancers, and chondrocyte cell death, indicating the involvement of CRF1 signaling in p53 regulation. In addition, numerous *in vitro* and *in vivo* studies conducted with cancer cell lines and *in vivo* experimental systems have reported on the actions of CRF and UCNs through their receptors: CRF1 and CRF2.

The effects of CRH and UCNs exerted through the CRF receptors are divided into roughly two groups: those exerting beneficial effects and those exerting adverse (including potentially adverse) effects. The reported studies can be summarized as follows:

1. Reports on the beneficial effects of CRH and UCNs

- 1) CRH and UCN I reduced cell proliferation and motility, and UCN I promoted neuron-like differentiation mediated by a downstream increase in p27^{Kip1}, as well as reduced c-Myc mRNA accumulation in the human neuroblastoma cell line SK-N-SH (N) [57].
- 2) CRH and UCN I inhibited transforming growth factor- β 1 signaling through CRF1, which led to the reduced migration of MCF-7 and MDA-MB-231 breast cancer cells. In addition, CRH and UCN II inhibited growth and promoted apoptosis in MCF-7 cells by regulating the expression and distribution of androgen and vitamin D receptors [58-61].
- 3) *In vitro* experiments have shown that CRF2/UCN II signaling inhibited the proliferation, migration, invasion, and colony formation of CRC cells expressing CRF2. In *in vivo* experiments, CRF2 xenografts resulted in decreased growth, reduced expression of epithelial to mesenchymal transition (EMT) inducers, and elevated levels of EMT suppressors [47]. In addition, CRF2 restoration might prove effective in managing CRC response to immune-mediated apoptotic stimuli [62].

- 4) CRH and UCN I stimulated TRP1 gene transcription. UCN I may exert anti-tumor actions in melanoma cells.
- 5) CRH, which exerts its action via both CRF1 and CRF2, reduced Bcl-2 expression and induced Bax expression, leading to hyperpolarization of the mitochondrial membrane potential to activate caspase-9 in the RM-1 and LNCaP prostate cancer cells [65].
- 6) UCN II exposure strikingly inhibited the growth of Lewis lung carcinoma (LLC) in *in vivo* experiments and directly inhibited the proliferation of LLC in *in vitro* experiments [66].
- 7) CRH and its analogs demonstrated exceptional potency in inhibiting Cloudman melanoma cell proliferation in culture and reduced net tumor volume of B16 melanoma cells in mice by 30%-60% compared to control animals [67].
- 8) It was reported that UCN II strikingly inhibited the vascularization of LLC [66]. In addition, UCN I inhibited the growth of HCC and reduced tumor microvessel density in nude mice, inhibited angiogenesis in human HCC tissues and proliferation of HUVECs, and decreased the expression of mRNA and plasma concentrations of vascular endothelial growth factor in an HCC transplanted mouse model [68].
- 9) UCN II significantly decreased CRF1 but increased CRF2 and directly decreased the mRNA levels of luteinizing hormone, follicle-stimulating hormone, and gonadotropin-releasing hormone receptor via CRF2 in mouse gonadotropic L β T2 tumor cells [44].

2. Reports on the potentially adverse effects of CRH and UCNs

- 1) UCN I promoted tumor cell migration by upregulating cytosolic phospholipase A2 (PLA2) expression via CRF1, but suppressed tumor cell migration by downregulating Ca²⁺-independent PLA2 expression via CRF2 in HCC, HepG2 cells, and SMMC-772 cells stably expressing both CRF1 and CRF2. This indicates that stimulation of CRF1 may exert adverse effects in cancer therapy of HCC [69].
- 2) UCN II, a specific agonist of CRF2, exerted proliferative actions in both RM-1 and LNCaP prostate cancer cells by increasing Bcl-2 expression and decreasing Bax expression [65].

- 3) CRH and especially UCN I stimulated GH release from primary cultures of GH-producing tumors obtained from two patients with acromegaly following transsphenoidal surgery [70].

These results indicated that although stimulation of CRF receptors may cause adverse events in some cancer patients, stimulating CRF receptor signaling may generally have potentially antagonistic actions against physiological properties of cancer and the supporting mechanisms of carcinogenesis. This indicates that CRF receptor agonists may exert anti-cancer properties or can be used as agents in adjuvant chemotherapy. Therefore, CRF receptor agonists may be applied for therapeutic options for anti-cancer therapy with special care to avoid such adverse actions by agents working through the CRF receptors.

Conclusion

CRH/UCNs and their receptors, i.e., CRF1 and CRF2, are widely distributed in both normal and cancer tissues. The effects of CRF receptors are diverse due to the combinations of the isoforms of CRF receptors, especially CRF1, the properties of the agents (e.g., either agonist or antagonist actions of these receptors), and the agents working on them. In addition, the effects of activated signaling pathways in target cancer cells and the variations of CRH/UCNs and related agents may, therefore, result both directly and indirectly in various outcomes of cancer therapies. These results indicate that CRH/UCNs and its related peptides-with giving careful attention to the possible latent adverse events through CRF receptors-may be potentially useful as direct or indirect suppressive agents for adjuvant cancer chemotherapy.

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