Inhibitory Effect of Corticotropin-Releasing Hormone on Fish Feeding (Postprint)

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Abstract

Corticotropin-releasing hormone (CRF) serves as a centrally regulated anorexigenic factor that induces satiety in fish, thereby reducing feed intake and weight gain rates. CRF is abundantly distributed in the hypothalamus, where it stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which subsequently triggers cortisol release, suppressing feeding behavior and energy metabolism. Based on research progress of CRF in mammals and certain fish species, this article elaborates on the discovery history and molecular structure of CRF, its regulatory effects on fish feeding and the underlying mechanisms, providing a theoretical basis for future research on fish feeding regulation, growth, and aquaculture production.

Full Text

Inhibitory Effects of Corticotropin-Releasing Hormone on Fish Feed Intake

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Abstract: Corticotropin-releasing hormone (CRF) functions as a centrally regulated anorexigenic factor that induces satiety in fish, thereby reducing feed intake and body weight gain. CRF is extensively distributed in the hypothalamus, where it stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH), which further triggers cortisol release to inhibit feeding and energy metabolism. Based on research progress regarding CRF in mammals and certain fish species, this review elaborates on the discovery history and molecular structure of CRF, its regulatory effects on fish feeding, and the underlying mechanisms, providing a theoretical foundation for future research on feeding regulation, growth, and production in fish.

Keywords: fish; feed intake; appetite factor; corticotropin-releasing hormone; cortisol

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Fish obtain nutrients and energy through feeding to promote growth and development [1]. Feeding regulation is complex and precise, with various peripheral appetite-related physical or chemical signals generating hunger or satiety signals that reach the central nervous system through neural or humoral pathways to modulate feeding [2]. Corticotropin-releasing hormone (CRF) functions as a centrally regulated satiety signal factor (anorexigenic factor). Its mature peptide contains 41 amino acids and can activate the hypothalamus-pituitary-interrenal (HPI) axis, causing the pituitary to release adrenocorticotropic hormone (ACTH) and affecting feeding behavior in animals [3-4]. CRF has become a research hotspot in the field of animal feeding and energy metabolism, with numerous studies reported in mammals but relatively few in fish. Therefore, based on current research status of CRF in mammals and some fish species, this paper elaborates on the discovery history, molecular structure, regulatory effects on fish feeding, and underlying mechanisms, focusing on reviewing the effects of exogenous CRF peptide administered through different injection methods or endogenous CRF modulators under various treatments on fish feeding, as well as interactions between CRF and its receptors, cortisol, and other appetite factors. This will provide a theoretical basis for future research on feeding regulation and growth in fish, as well as for practical applications in aquaculture.

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In 1955, Saffran et al. [5] demonstrated increased ACTH release when rat pituitary cells were cultured in vitro and stimulated with hypothalamic extracts, leading to the naming of this factor as CRF. In 1981, Vale et al. [4] successfully extracted and purified a 41-amino-acid CRF peptide from sheep hypothalamus. Building upon this work, Furutani et al. [6] further elucidated the structure of the CRF gene in 1983. CRF is primarily located in the hypothalamus and stimulates ACTH secretion from the pituitary. Based on reports from mammals and fish, as well as identification in chickens, Vandenborne et al. [7] summarized the CRF gene structure, which contains two exons and one intron. Exon 1 contains the 5' untranslated region, while exon 2 contains the coding region and 3' untranslated region (Figure 1 [Figure 1: see original paper]). In fish, the CRF gene cDNA is 0.9–1.0 kbp in length, with the coding region typically spanning 0.4–0.5 kbp. The amino acid structure encoded by the CRF coding region includes a hydrophobic signal peptide, a conserved peptide of

unproven function in the middle segment, and a C-terminal mature peptide comprising 41 amino acid residues. Activation of two sites at the C-terminus (amide groups) confers CRF activity. The CRF gene has been found to contain two isoforms (CRF1 and CRF2) in white sucker (*Catostomus commersonii*) [8], goldfish (*Carassius auratus*) [9], sockeye salmon (*Oncorhynchus nerka*) [10], rainbow trout (*Oncorhynchus mykiss*) [11], and common carp (*Cyprinus carpio*) [12], whereas no isoforms were detected in tilapia (*Oreochromis mossambicus*) [13], flounder (*Platichthys flesus*) [14], zebrafish (*Barchydanio rerio* var) [15], or qingbo (*Schizothorax prenanti*) [16].

prohormone: prohormone; Mature peptide: mature peptide; Exon 1: exon 1; Exon 2: exon 2; Intro: intron; 5' URT: 5' untranslated region; 3' URT: 3' untranslated region; CDS: coding sequence.

Figure 1 The structure of the CRF gene [Figure 1: see original paper]

2 CRF Regulation of Fish Feeding

Based on its structure and distribution, CRF plays a crucial regulatory role in the appetite control endocrine system of fish. Studies investigating the effects of exogenous CRF peptide administered through various injection methods on fish feeding, or examining changes in endogenous CRF expression levels and feeding under different treatments, have demonstrated that CRF can regulate feed intake in fish.

2.1.1 Central Injection of CRF Regulates Fish Feeding

Studies investigating changes in feed intake following central (intracerebroventricular) injection of CRF in mammals have consistently demonstrated that CRF suppresses feeding through central administration [17-18]. In fish, the regulatory effects of central CRF injection on feeding have only been examined in goldfish. De Pedro et al. [19] reported that central injection of CRF in goldfish after 24 h of fasting reduced feed intake within 2 h post-injection, suggesting that CRF may inhibit feeding through the central system in goldfish. Matsuda et al. [17] confirmed in goldfish that pretreatment with the CRF receptor antagonist h-CRF(9-41) could reverse the effects of CRF injection. In summary, central injection of CRF exerts an inhibitory effect on feeding in goldfish, and this effect can be reversed by pretreatment with h-CRF(9-41).

2.1.2 Peripheral Injection of CRF Regulates Fish Feeding

Limited available studies in mammals and fish have shown that peripheral injection of CRF does not significantly alter feed intake but exhibits a decreasing trend [19-20]. In fish, De Pedro et al. [19] administered intraperitoneal injections of CRF in goldfish and observed a decreasing trend in feed intake, suggesting that peripheral CRF may affect feeding in goldfish. These experiments involved single peripheral injections lasting only one day, with no reports of long-term

peripheral injections, making it unclear whether long-term peripheral CRF injection suppresses feeding in fish.

Although reports on peripheral CRF injection for feeding regulation are scarce, studies have documented the distribution of peripheral CRF and CRF-related peptides in the gastrointestinal system of rodents, showing that CRF and CRF-related peptides are present in small amounts in peripheral tissues [21-22]. Taché et al. [23] proposed that direct or indirect stimulation of the gastrointestinal tract in rodents can elevate peripheral CRF and CRF-related peptide levels, thereby inhibiting feed intake. This suggests that peripheral CRF and CRF-related peptides in rodents play an important regulatory role in stress-induced alterations in intestinal motility. In fish, Pepels et al. [24] detected CRF in the blood of stressed Nile tilapia (*Oreochromis niloticus*), indicating that CRF may also be present in the peripheral system of fish.

2.2.1 Regulation of CRF by Different Feeding Status

Fasting reduces CRF gene expression levels in rodents [25]. In fish, current reports are limited to goldfish and qingbo. Maruyama et al. [26] conducted a 7-day experiment with three groups of goldfish, revealing that compared to the normal feeding group, the fasting group showed a decreasing trend in brain CRF gene expression, though not statistically significant, while the overfeeding group exhibited a significant increase. Wang et al. [16] subjected qingbo to short-term (1 day) fasting, which showed no significant change in hypothalamic CRF gene expression levels; however, after long-term (7 days) fasting, hypothalamic CRF gene expression levels decreased significantly and recovered by day 9 of refeeding. In summary, long-term fasting can cause CRF to function as an anorexigenic factor that inhibits feeding in fish.

2.2.2 Regulation of CRF by Environmental Factors

Environmental factors affecting fish growth and development primarily include dissolved oxygen saturation, ammonia levels, and osmotic capacity. Lower oxygen saturation, increased ammonia, and elevated osmotic pressure can inhibit fish feeding while increasing CRF gene expression levels, suggesting that CRF can function as an anorexigenic factor to regulate feeding under different environmental conditions.

Short-term hypoxia enables CRF to exert anorexigenic effects in fish, whereas long-term hypoxia reduces this anorexigenic regulatory function. Bernier et al. [27] exposed rainbow trout to 50% or 35% oxygen saturation for 24 h, demonstrating that both forebrain CRF gene expression levels and feed intake decreased in a manner positively correlated with the degree of hypoxic treatment. Furthermore, after long-term (72 h) hypoxic treatment, the magnitude of decrease in forebrain CRF gene expression and its anorexigenic regulatory effect showed a diminishing trend.

Regarding ammonia treatment, although Wood [28] suggested that low levels of

exogenous ammonia have no significant effect on fish feeding, Ortega et al. [29] found that chronically increased ammonia in water caused a dose-dependent reduction in feed intake and increased CRF gene expression levels in rainbow trout. Craig et al. [30] observed that compared to freshwater-reared fish, rainbow trout in seawater exhibited increased brain CRF expression levels and decreased feed intake, indicating that elevated osmotic pressure may enable CRF to function as an anorexigenic factor.

3 Mechanisms of CRF Regulation of Fish Feeding

The mechanisms by which CRF regulates feeding in animals, including fish, are complex and primarily involve three pathways: (1) CRF binding to receptors to exert appetite regulatory effects; (2) CRF activating the release of downstream cortisol through the HPI axis to regulate feeding; and (3) CRF directly or indirectly regulating feeding by interacting with other appetite modulators (Figure 2 [Figure 2: see original paper]). These three mechanisms can also interact with each other to collectively influence feeding behavior.

CRF: corticotropin-releasing hormone; CRFR1: corticotropin-releasing hormone receptor 1; CRFR2: corticotropin-releasing hormone receptor 2; POMC: proopiomelanocortin; CART: cocaine- and amphetamine-regulated transcript; NPY: neuropeptide Y; AgRP: agouti-related protein; -MSH: -melanocyte-stimulating hormone; MC4R: melanocortin 4 receptor; Ghrelin: ghrelin; ACTH: adrenocorticotropic hormone. Solid arrows indicate stimulatory effects; dashed arrows indicate inhibitory effects.

Figure 2 Mechanisms of CRF regulation of feeding [Figure 2: see original paper]

3.1 CRF Binding to Receptors Inhibits Fish Feeding

In mammals, CRF can directly bind to CRF receptor 2 (CRFR2) to exert anorexigenic effects, whereas binding to CRF receptor 1 (CRFR1) has no impact on feeding regulation. In fish, however, the CRF system may utilize different pathways to regulate feeding. Vaughan et al. [31] reported that the CRF-related peptide urotensin I (UI) and CRF both bind to CRFR2 with equal affinity to inhibit feeding. Bernier et al. [32] found that central injection of UI in goldfish reduced feed intake more effectively than central injection of CRF, suggesting that in fish, CRF and UI may non-selectively bind to CRFR2 to exert anorexigenic effects, or that CRF may regulate feeding by binding to either CRFR1 or CRFR2.

The primary brain regions where CRF binds to receptors are the preoptic nucleus (NPO) and the lateral tuberal nucleus (NLT) [33]. Arai et al. [34] also identified small amounts of CRFR1 in the brainstem of catfish (*Silurus asotus*), suggesting that central CRF may influence feeding through brainstem neuronal circuits involved in regulating gastrointestinal motility. Cardoso et al. [35] detected trace amounts of CRFR1 in the intestine of pufferfish (Tetraodontidae), and Martínez et al. [36] demonstrated through peripheral CRF injection in mice

that trace amounts of CRF receptors exist in the gastrointestinal system and bind with CRF to stimulate intestinal motility changes that regulate feeding.

3.2 CRF Activates Cortisol, the Terminal Product of the HPI Axis, to Regulate Fish Feeding

In the HPI axis, CRF released from the hypothalamus stimulates the pituitary to release ACTH, which further activates the release of the glucocorticoid cortisol from the interrenal gland. Cortisol directly regulates fish feeding or indirectly modulates it through interactions with other endocrine regulatory pathways and gastrointestinal nutrient absorption.

Several studies have reported that cortisol, as a glucocorticoid, can inhibit feeding. Gregory et al. [37] demonstrated that elevating plasma cortisol levels in rainbow trout suppressed feed intake. However, increased cortisol can negatively feedback on CRF, diminishing the anorexigenic effects of CRF. Further research has shown that CRF can regulate the effects of cortisol on feeding through interactions with other endocrine pathways. Bernier et al. [38] found that moderate, chronic elevation of plasma cortisol in goldfish increased feed intake, decreased forebrain CRF gene expression, and elevated NPY gene expression. Further increasing cortisol concentration reduced CRF gene expression but had no effect on NPY gene expression, while feed intake showed a decreasing trend. The release of glucocorticoid cortisol triggered by CRF can indirectly influence feeding through intestinal nutrient absorption. Ducouret et al. [39] reported that glucocorticoid receptors are present in the gastrointestinal tract of fish, and Vllette et al. [40] found that cortisol enhances intestinal Na+/K+-ATPase activity.

3.3 CRF Interacts with Other Appetite Regulators to Control Fish Feeding

After binding to receptors, CRF can interact with the central appetite control nervous system or with peripheral appetite regulatory factors through blood circulation to transmit satiety signals. CRF interacts with central appetite control neural system regulators, including hypothalamic proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART), neuropeptide Y (NPY)/agouti-related protein (AgRP), the POMC-derived peptide -melanocyte-stimulating hormone (-MSH) that regulates animal feeding, and melanocortin 4 receptor (MC4R) to regulate fish feeding. CRF also interacts with peripheral appetite regulators including ghrelin secreted by the gastrointestinal tract and insulin secreted by the pancreas to control fish feeding. Additionally, CRF can interact with apelin to regulate fish feeding.

3.3.1 Interaction of CRF with POMC/CART or NPY/AgRP Regulates Feeding In vitro and in vivo experiments in rats have demonstrated that the CRF system can upregulate POMC/CART to participate in anorexigenic actions, and POMC/CART activates the HPI axis through the CRF system

[41]. Conversely, NPY/AgRP can downregulate CRF-mediated feeding regulation, and the interaction between NPY/AgRP and CRF is also closely related to glucocorticoids. Heinrichs et al. [42] co-injected NPY and the CRF receptor antagonist h-CRF(9-41) into the paraventricular nucleus region of the rat hypothalamus, resulting in increased feed intake. Subsequently, in rats pretreated with the glucocorticoid dexamethasone, central injection of NPY downregulated CRF gene expression in the paraventricular nucleus and increased feed intake. Reports in fish are still limited, with current research only available in goldfish. In goldfish, Bernier et al. [38] found that slowly and moderately increasing plasma cortisol concentration stimulated NPY release, inhibited CRF gene expression, and increased feed intake.

3.3.2 Interaction of CRF with -MSH and MC4R Regulates Feeding As a neuropeptide that integrates anorexigenic signals, CRF incorporates -melanocyte-stimulating hormone (-MSH), a POMC-derived peptide that regulates animal feeding, and its receptor MC4R to control feeding [43]. The interaction between CRF and the melanocortin system has only been reported in goldfish among fish species. Matsuda et al. [44] co-injected the -MSH agonist (MTII) and h-CRF(9-41) into the goldfish brain, finding that the appetite-suppressing effect induced by MTII was diminished. However, co-injection of CRF and the MC4R antagonist HS024 had no significant effect on feed intake in goldfish. Further immunohistochemical analysis detected CRF and MSH neurons in the brain, with -MSH-containing nerve fiber terminals closely associated with CRF neurons in the hypothalamic region. Collectively, these findings suggest that in fish, -MSH and MC4R exert anorexigenic effects through the CRF signaling pathway.

3.3.3 Interaction of CRF with Ghrelin and Insulin Regulates Feeding The CRF signaling pathway enables the peripheral appetite regulator ghrelin to suppress appetite, and because ghrelin participates in glucose metabolism, interactions among CRF, ghrelin, and insulin affect animal feeding. Combined action of ghrelin and CRF can reduce insulin sensitivity. Solomon et al. [45] pretreated rats with intravenous injection of 0.5 mL ghrelin-specific and non-specific antibodies, followed by subcutaneous injection of saline, insulin, and 2-deoxyglucose. Immunohistochemical detection revealed that the CRF-positive neuron count in the insulin and ghrelin antibody co-treatment group was higher than in the insulin-only group. Compared to the non-specific antibody pretreatment group, both insulin-treated and 2-deoxyglucose-treated groups showed significantly higher CRF c-fos (an immediate early gene) positive neurons than the saline control group, yet feed intake was significantly increased compared to the control group. This paradoxical phenomenon in CRF anorexigenic signaling following insulin treatment suggests that low blood glucose stress may activate the HPI axis to compensate for glucose levels, stimulating the production of small amounts of ACTH and cortisol, which can promote feeding. In fish, Jönsson et al. [46] conducted central injections in juvenile rainbow trout divided into

four groups: the ghrelin group showed significantly reduced feed intake, the h-CRF(9–41) group showed no significant change, while the co-injection group exhibited a trend toward increased feed intake compared to the ghrelin group, with intake levels comparable to the control group. These results suggest that ghrelin inhibits feeding in fish through the CRF system.

3.3.4 Interaction of CRF with Apelin Regulates Feeding Limited reports exist on the interaction between CRF and apelin in feeding regulation. Apelin can stimulate CRF release and inhibit feeding in mammals through the CRF system [47-48]. Lv et al. [48] fasted male mice for 24 h and then centrally injected 0.3, 1.0, and 3.0 g/kg apelin-13, with the control group receiving saline. The results showed dose-dependent suppression of feed intake in the treatment groups compared to the control. In a further experiment with four groups of mice, compared to the saline control group, the h-CRF(9-41) treatment group showed no significant change in 4 h feed intake, while the apelin-13 treatment group exhibited extremely significant reduction in cumulative feed intake. However, the co-injection group receiving both apelin-13 and h-CRF(9-41) showed no significant difference in feed intake compared to the control group, and significantly increased intake compared to the apelin-13-only group. The interaction between CRF and apelin has not yet been reported in fish.

4 Summary

Fish obtain nutrients and energy through feeding to promote their growth, development, and reproduction. Feeding regulation is complex and precise, involving interactions between central and peripheral anorexigenic and orexigenic factors that control feeding behavior. CRF serves as an important centrally regulated anorexigenic factor and represents a major research focus in the field of animal feeding and energy metabolism. Currently, studies on CRF-mediated feeding regulation and mechanisms have primarily concentrated on mammals, with limited research in fish. Due to the diverse environments fish inhabit and their considerable physiological and functional differences, future research should build upon mammalian findings to deeply investigate the feeding regulatory mechanisms of CRF in different fish species, providing a theoretical basis for feeding regulation and practical applications in aquaculture.

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Note: Figure translations are in progress. See original paper for figures.