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The corticotropin-releasing factor system as a mediator of the appetite-suppressing effects of stress in fish

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Abstract

A characteristic feature of the behavioural response to intensely acute or chronic stressors is a reduction in appetite. In fish, as in other vertebrates, the corticotropin-releasing factor (CRF) system plays a key role in coordinating the neuroendocrine, autonomic, and behavioural responses to stress. The following review documents the evidence implicating the CRF system as a mediator of the appetite-suppressing effects of stress in fish. Central injections of CRF or the related peptide, urotensin I (UI), or pharmacological treatments or stressors that result in an increase in forebrain CRF and UI gene expression, can elicit dose-dependent reductions in food intake that are at least partially reversed by pre-treatment with a CRF receptor antagonist. In addition, the appetite suppressing effects of various environmental, pathological, physical, and social stressors are associated with elevated levels of forebrain CRF and UI gene expression and with an activation of the hypothalamic–pituitary–interrenal (HPI) stress axis. In contrast, although stressors can also be associated with an increase in caudal neurosecretory system CRF and UI gene expression and an endocrine role for CRF-related peptides has been suggested, the physiological effects of peripheral CRF-related peptides on the gastrointestinal system and in the regulation of appetite have not been investigated. Overall, while CRF and UI appear to participate in the stress-induced changes in feeding behaviour in fish, the role of other know components of the CRF system is not known. Moreover, the extent to which the anorexigenic effects of CRF-related peptides are mediated through the hypothalamic feeding center, the HPI axis and cortisol, or via actions on descending autonomic pathways remains to be investigated.

Keywords: Anorexia; Cortisol; CRF; Feeding behaviour; Hypothalamic–pituitary–interrenal axis; Stress; Urotensin I

1. Introduction

Recent advances in the field of comparative stress physiology suggest that the corticotropin-releasing factor (CRF) system in vertebrates plays a key role in regulating and integrating the neuroendocrine, autonomic, immune, and behavioural responses to stressors (Crespi and Denver, 2004; Heinrichs, 2005; Lovejoy and Balment, 1999). Progress on whole-genome sequencing projects has also shown that the components of the CRF system in vertebrates are highly conserved (Chang and Hsu, 2004). In fish, the CRF system is comprised of four related neuropeptides, CRF (Okawara et al., 1988), urotensin I (UI; Lederis et al., 1982), and orthologs of mammalian urocortin 2 and 3 (Chang and Hsu, 2004; Lewis et al., 2001), two main receptor types, CRF-R1 and -R2 (Arai et al., 2001; Chang and Hsu, 2004; Pohl et al., 2001), and a binding protein, CRF-BP (Doyon et al., 2005; Huising et al., 2004). While the CRF system in fish is primarily known for its role in the control of the hypothalamic–pituitary–interrenal (HPI) stress axis (Huising et al., 2004; Lederis et al., 1994; Wendelaar Bonga, 1997; see review by Flik et al. in this volume), it has also been implicated in several other physiological processes. Accumulating evidence in a few teleost species suggest that CRF-related peptides are involved in the autonomic regulation of the cardiovascular system (see review by Le Mevel et al. in this volume), the communication between the

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immune and neuroendocrine systems (Volkoff and Peter, 2004; Pepels et al., 2004a), the control of locomotor activity (Clements et al., 2003, 2002; Clements and Schreck, 2004), and the regulation of food intake—the focus of this review.

The control of food intake in fish (see reviews by De Pedro and Bjornsson, 2001; Jensen, 2001; Le Bail and Boeuf, 1997; Lin et al., 2000; Volkoff et al., 2005), amphibians (Carr et al., 2002), birds (Denbow, 1999; Kuenzel et al., 1999), and mammals (Berthoud, 2002), involves the detection and integration of a complex mix of information by a distinct hypothalamic neuronal circuitry. While several areas of the brain from the telencephalon to the medulla are involved in the central control of feeding behaviour in fish, electrical stimulation of the inferior lateral lobes in the hypothalamus evokes the most consistent and low-threshold feeding responses (Demski, 1981, 1983; Peter, 1979). In general, the hypothalamic feeding centre integrates peripheral signals related to gastrointestinal content and energy reserves, sensory information such as olfactory and gustatory cues, and central signals related to the behavioural state of the animal including its perception of immediate or chronic stressors (Berthoud, 2002; Woods et al., 1998). In return the hypothalamus produces several orexigenic (appetite-stimulating) and anorexigenic (appetite-inhibiting) signals that regulate feeding responses via specific motor pathways and modulate the processes of digestion, absorption, and metabolite utilization via several autonomic and endocrine pathways (Kalra et al., 1999).

The appetite-suppressing effects of intensely acute or chronic stressors have been well documented across multiple vertebrate lineages (Bernier and Peter, 2001a; Carr, 2002; Chrousos and Gold, 1992). In mammals, considerable evidence suggests a role for the CRF system in appetite regulation and energy balance during conditions of threatened homeostasis (Heinrichs, 2005; Heinrichs and Richard, 1999; Richard et al., 2002; Zorrilla and Koob, 2005). Similarly, the conserved effects of CRF-related peptides on food intake in birds (Denbow et al., 1999; Zhang et al., 2001), amphibians (Carr et al., 2002; Crespi et al., 2004), and fishes (Bernier and Peter, 2001b; De Pedro et al., 1993), suggest that the role of the CRF system in the control of food intake maybe evolutionary conserved. Toward a synthesis of the evidence implicating the CRF system in the regulation of food intake in fish and as a means of highlighting areas of research on the CRF system that have yet to be explored in these animals, this paper will review: (a) the effects of CRF-related peptides on food intake; (b) the evidence implicating CRF-related peptides as mediators of the appetite-suppressing effects of stressors; and (c) the interactions of CRF-related peptides with other neuroendocrine signals implicated in the regulation of food intake.

2. Effects of CRF-related peptides on food intake

2.1. Central effects

Intracerebroventricular (icv) injections of CRF and UI in goldfish (*Carassius auratus*; Bernier and Peter, 2001b; De Pedro et al., 1993), as in other vertebrates (Britton et al., 1982, 1984; Crespi et al., 2004; Denbow et al., 1999; Krahn et al., 1988; Zhang et al., 2001), elicit dose-dependent reductions in food intake. While central injections of the CRF-related peptides urocortin 2 and 3 also have an inhibitory action on food intake in rodents (Inoue et al., 2003; Pelleymounter et al., 2004) their effects on the regulation of food intake in fish are not known. In mammals, since the appetite-suppressing effects of CRF-related peptides can be blocked with CRF-R2 but not CRF-R1 selective antagonists (Pelleymounter et al., 2000; Smagin et al., 1998), the CRF-R2 subtype is thought to play a primary role in mediating the anorectic effects of CRF-related peptides (Richard et al., 2002). In fish, while the appetite-suppressing effects of icv CRF and UI are reversed by the specific but non-selective CRF receptor antagonist, α-helical $CRF_{(9–41)}$ (Bernier and Peter, 2001b; De Pedro et al., 1997), the CRF receptor subtype(s) mediating the anorectic effects of CRF-related ligands have yet to be identified. Although icv UI is significantly more potent than CRF in reducing food intake in goldfish (Bernier and Peter, 2001b) and rats (Spina et al., 1996), and these results are consistent with the binding profile of UI and CRF at the mammalian CRF-R2 receptor (Vaughan et al., 1995), evidence to date suggest that CRF-R1 and -R2 in fish may not discriminate between CRF and UI (Arai et al., 2001; Pohl et al., 2001). Results from experiments using brain implants of α-helical $CRF_{(9–41)}$ also indicate that endogenous CRF-related peptides in fish have anorexigenic properties. Pre-treatment of goldfish with the CRF receptor antagonist reverses the reduction in food intake induced by intraperitoneal implants of the glucocorticoid receptor antagonist, RU-486, or the cortisol synthesis inhibitor, metyrapone, pharmacological treatments that elevate forebrain CRF and UI gene expression (Bernier and Peter, 2001b).

The central sites of the anorectic actions of CRF-related peptide in fish are not known. However, available evidence suggests that likely appetite-regulating regions of the CRF system in fish include the hypothalamic nucleus preopticus (npo), nucleus lateralis tuberis (nlt), and nucleus recessus lateralis (nrl; Fig. 1). In the catfish brain (Arai et al., 2001), CRF-R2 is expressed in the npo and nlt, two nuclei with CRF-related peptide expression and immunoreactivity in fish (Ando et al., 1999; Coto-Montes et al., 1994; Matz and Hofeldt, 1999; Okawara et al., 1992; Olivereau and Olivereau, 1988a; Olivereau et al., 1984; Pepels et al., 2002; Yulis et al., 1986; Zupanc et al., 1999) and regions where several orexigenic and anorexigenic neuropeptides are expressed (Cerda-Reverter and Peter, 2003; Cerda-Reverter et al., 2003; Peng et al., 1994; Unniappan et al., 2004). The npo and nlt are thought to be the teleostean homolog of the mammalian paraventricular and arcuate nuclei, respectively, two important cell groups known to contribute extensively to the regulation of feeding (Berthoud, 2002; Kalra et al., 1999). The nrl is also immunoreactive for CRF-related peptides (Okawara et al., 1992; Olivereau and Olivereau, 1988a; Pepels et al., 2002), is involved in relaying

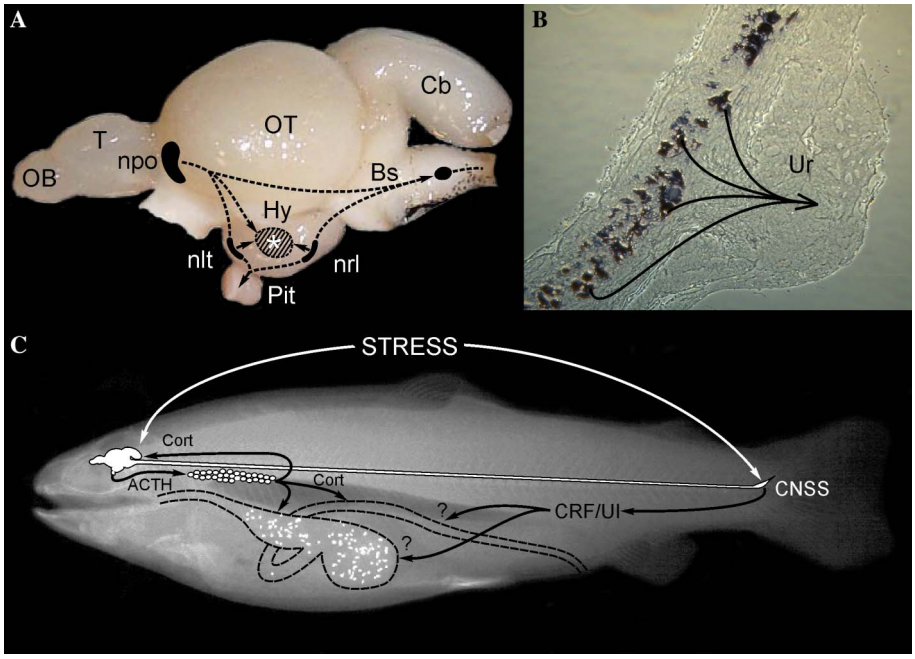

Fig. 1. Central and peripheral pathways of the CRF system postulated to contribute to the appetite-suppressing effects of stressors in rainbow trout. (A) Schematic sagittal view depicting the relationship between the primary sites of CRF-related peptide expression in the forebrain, the npo, nlt, and nrl, the hypothalamic-centered feeding neurocircuitry (∗), the CRF-related peptide fibers that synapse with descending autonomic pathways, and the fibers that terminate in the pituitary. (B) Phase contrast micrograph of midsagittal section through the CNSS hybridized with an antisense DIG-labelled UI riboprobe. The UI gene expression pattern in the neurosecretory Dahlgren cells extends through the caudal most portion of the spinal cord. Nerve axons projecting from these cells and CRF-expressing Dahlgren cells project caudally through the urophysis terminating on capillaries that drain into the caudal vein. (C) X-ray image of a trout fed a labelled diet and overlaid with a diagrammatic representation of the CNS, the interrenal cells in the headkidney, and an outline of the gastrointestinal system. Stress signals are integrated by CRF-related peptide neurons in the forebrain and the CNSS. CRF-related peptides of hypothalamic origin regulate pituitary ACTH secretion and ACTH drives cortisol synthesis and secretion from the interrenal cells. Cortisol may impact food intake through its negative feedback effects on forebrain CRF and UI and via actions on the gastrointestinal system. Finally, circulating CRF and UI of CNSS origin may affect food intake through direct actions on gastric and intestinal functions. Abbreviations: ACTH, adrenocorticotropic hormone; Bs, brainstem; CNSS, caudal neurosecretory system; Cb, cerebellum; Cort, cortisol; CRF, corticotropin-releasing factor; Hy, hypothalamus; nlt, nucleus lateralis tuberis; npo, nucleus preopticus; nrl, nucleus recessis lateralis; OB, olfactory bulbs; OT, optic tectum; T, telencephalon; UI, urotensin I; Ur, urophysis. (B) Reprinted with permission from Craig et al. (2005).

visceral and sensorial information in fish (Peter, 1979; Rink and Wullimann, 1998; Yoshimoto et al., 1998), and electrical stimulation of this nuclei is known to affect feeding behaviour (Demski, 1983).

In mammals, while several hypothalamic nuclei are possible loci for the anorectic actions of the CRF system (Richard et al., 2002), central CRF-related peptides can also affect food intake by modulating the brainstem neuronal circuitry involved in regulating gastrointestinal motor functions. Icv CRF or urocortin 1 inhibit gastric emptying by suppressing vagal activity (Kihara et al., 2001; Tache et al., 1999) and stimulate colonic motility by activating the sacral parasympathetic system (Tache et al., 2001). Whether, central CRF-related peptides play similar roles in fish is not known. However, CRF-R1 are expressed in the brainstem of catfish (Arai et al., 2001) and goldfish (N.J. Bernier, L. Wyngaarden, and R.E. Peter, unpublished observations), and there is anatomical (Arai et al., 2001; Batten et al., 1990; Pepels et al., 2002; Yulis et al., 1986) and physiological (Mimassi et al., 2003, 2000) evidence suggesting that CRF-related peptides in fish are involved in regulating descending autonomic pathways.

2.2. Peripheral effects

Although De Pedro et al. (1993) observed that intraperitoneal injections of ovine CRF do not affect food intake in goldfish, the physiological effects of peripheral CRF-related peptides on the gastrointestinal system in fish have not been investigated. However, unique features of the CRF system in fish (Pepels et al., 2004b; Winter et al., 2000) and the presence of plasma CRF (Pepels et al., 2004b) and UI (Suess et al., 1986) suggest an endocrine role for circulating CRF-related peptides (Fig. 1). The CRF system in all ray-finned fishes (Lovejoy and Balment, 1999), unlike other vertebrates, possess a major source of CRF and UI that can release its content to the circulation, the caudal neurosecretory system (CNSS; Craig et al., 2005; Lu et al., 2004). Moreover, in Acanthopterygii, the more derived bony fishes, CRF production in the lateral part of the ventral telencephalon may also be a significant source of circulating CRF (Pepels et al., 2002, 2004b). To date, neither CRF-R1 nor -R2 appear to be expressed in the gut of catfish (*Ameiurus nebulosus*; Arai et al., 2001) or chum salmon (*Oncorhynchus keta*; Pohl et al., 2001), but low levels of CRF-R1

expression have been detected in the intestine of pufferfish (*Fugu rubripes*; Cardoso et al., 2003) and goldfish (N.J. Bernier, L. Wyngaarden, and R.E. Peter, unpublished observations). In contrast, peripheral CRF-related peptides in mammals are known to contribute to the regulation of appetite during stress via direct gastrointestinal actions (Tache and Perdue, 2004). Urocortin 1, 2, and 3 are expressed in the enteric nervous system and gastrointestinal tract of rodents (Harada et al., 1999; Hsu and Hsueh, 2001; Lewis et al., 2001; Kozicz and Arimura, 2002) and these peripheral sources of CRF-related peptides play a role in stress-related alterations of gut motility (Tache et al., 2001). In general, peripheral administration of CRF-related peptides inhibit gastric emptying and delay small intestinal transit by activating CRF-R2 receptors, and stimulate colonic motility by activating CRF-R1 receptors (Martinez et al., 2002; Zorrilla et al., 2003).

3. CRF-related peptides as mediators of the appetite-suppressing effects of stressors

A variety of different types of stressors suppress food intake in fish (Bernier and Peter, 2001a; Schreck et al., 1997; Wendelaar Bonga, 1997). This includes systemic stressors such as environmental, pathological, or physical stressors that are characterized by an immediate threat to homeostasis, and processive stressors such as social subordination and isolation that require sequential stimulus assembly and interpretation by higher brain structures (Herman and Cullinan, 1997). While systemic and processive stressors involve the recruitment of separate stress-sensitive neurocircuitries, they both culminate in the activation of the hypothalamic–pituitary adrenal axis and the secretion of glucocorticoids (Herman et al., 2003). Similarly, most forms of appetite-suppressing stressors in fish involve the recruitment of the HPI axis and evidence from several recent studies now suggests that CRF-related peptides are implicated in this behavioural response (Table 1).

3.1. Environmental stressors

Chronic exposure to hypoxia in fish is characterized by a reduction in food intake (Buentello et al., 2000; Chabot and Dutil, 1999; Pichavant et al., 2001; Zhou et al., 2001) and recent evidence suggests that endogenous CRF-related peptides contribute to the regulation of appetite under these conditions (Bernier and Craig, 2005). In rainbow trout (*Oncorhynchus mykiss*) exposed to 50 or 35% O_2 saturation for 24 h, preoptic area CRF and UI gene expression is positively correlated with the severity of the hypoxia-induced appetite suppression. Most significantly, CRF receptor blockade with α-helical $CRF_{(9–41)}$ partially reverses the reduction in food intake and prevents the increase in plasma cortisol associated with exposure to 24 h 35% O_2 saturation. Whether CRF-related peptides are also involved in mediating the sustained anorexia that characterizes chronic hypoxia in fish is less clear since the relationship between the anorexic effects of hypoxia and the forebrain mRNA levels of CRF and UI breaks down after 72 h of hypoxia exposure (Bernier and Craig, 2005).

Correlative evidence between the forebrain mRNA levels of CRF, UI, and food intake also implicates CRF-related peptides as potential mediators of the appetite-suppressing effects of ammonia in fish (Ortega et al., 2005). Although low levels of exogenous ammonia have no effect on food intake (Wood, 2004), above a certain species-specific threshold, chronic increases in water ammonia elicit an initial dose-dependent reduction in food intake followed by a gradual recovery (Beamish and Tandler, 1990; Ortega et al., 2005; Wicks and Randall, 2002). Similarly, in rainbow trout, chronic hyperammonemia elicits transient increases in telencephalon CRF and UI mRNA levels, hypothalamus UI mRNA levels, and plasma cortisol concentrations that correspond with the transient nature of the appetite suppression (Ortega et al., 2005).

Salinity is another environmental factor known to affect feeding in fish (De Boeck et al., 2000; Rubio et al., 2005) and in several salmonid species, abrupt transfer from fresh water (FW) to seawater (SW) is accompanied by a temporary decrease in food intake (Arnesen et al., 1993; McKay and Gjerde, 1985; Usher et al., 1991). In rainbow trout, the appetite-suppressing effects of SW transfer are also associated with a significant, but differential, up-regulation of forebrain and CNSS CRF and UI gene expression (Craig et al., 2005). More specifically, while SW transfer in trout chronically suppressed food intake over a 2-week period, it transiently increased CRF mRNA levels in the hypothalamus and preoptic region, and elicited a delayed increase in hypothalamic UI mRNA levels and chronic elevations in CNSS CRF and UI gene expression. Therefore, although more direct evidence is needed, in addition to the proposed osmoregulatory roles of the CRF system in fish (Lovejoy and Balment, 1999), the above findings suggest that CRF and UI may serve as regulators of food intake during the response to osmotic stress.

3.2. Pathological stressors

Anorexia is a characteristic response in fish to a variety of different viral (Byrne et al., 1998; Damsgard et al., 1998), bacterial (Damsgard et al., 2004; Pirhonen et al., 2000), and parasitic (Chin et al., 2004) infections. This infection-induced loss of appetite may represent an active defence mechanism of the host as in many cases it has been shown to reduce the severity of the disease and increase survival (Damsgard et al., 1998; Li and Woo, 1991; Pirhonen et al., 2003; Wise and Johnson, 1998). While little is known about the neuroendocrine pathways that mediate the anorexic state of diseased fish, there is indirect evidence suggesting that CRF-related peptides may be implicated in this behavioural response to pathological stressors. The increase in plasma cortisol associated with the acute phase response of many fish diseases (Damsgard et al., 2004; Mesa et al., 2000; Olsen et al., 1992) suggest that central CRF-related

Table 1
Stressors in fish where a reduction in food intake has be associated with an activation of the CRF system and/or a recruitment of the hypothalamic–pituitary–interrenal axis as reflected by changes in plasma cortisol

Stressor	Effect on feeding	Effect on CRF system	Effect on plasma cortisol
Environmental			
Hypoxia	Sustained decrease[a]	Transient increase in POA CRF and UI mRNA levels[a]	Sustained increase[a]
Ammonia exposure	Transient decrease[b]	Region-, dose-, and time-dependent increase in forebrain CRF and UI mRNA levels[b]	Transient increase[b]
FW to SW transfer	Sustained decrease[c]	Transient increase in POA and HYP CRF, delayed increase in HYP UI, and sustained increase in CNSS CRF and UI mRNA levels[c]	Transient increase[c]
Pathological			
LPS challenge	Rapid decrease[d]	Increase in HYP and TEL CRF mRMA levels[d]	Transient increase[e]
Physical			
Chasing[f,h]	Sustained decrease after daily physical disturbance for 42 days[f]		Decrease after daily physical disturbance for 42 days[f]
Restraint[f,g,i]	Transient decrease after physical disturbance for 2 min[g]		Transient increase 2 h after physical disturbance for 2 min[g]
Handling[g]		Increase in POA CRF mRNA levels 6 h after repeated chasing[h]	Increase 6 h after repeated chasing[h]
		Increase in HYP CRF mRMA levels after 24 h restraint[i]	Increase after 24 h restraint[i]
Social			
Subordination	Sustained decrease[j]	Increase in POA CRF mRNA levels after 72 h interaction[k]	Increase after 72 h interaction[k]
Isolation	Sustained decrease[l]	Transient increase in POA CRF mRNA levels with isolation in 120 L tanks; sustained increase in POA CRF mRNA levels with isolation in 1.5 L tanks[h]	Transient increase[h]

Abbreviations used: CNSS, caudal neurosecretory system; CRF, corticotropin-releasing factor; FW, fresh water; HYP, hypothalamus; LPS, lipopolysaccharide; POA, preoptic area; SW, seawater; TEL, telencephalon; UI, urotensin I.

[a] Bernier and Craig (2005).
[b] Ortega et al. (2005).
[c] Craig et al. (2005).
[d] Volkoff and Peter (2004).
[e] Haukenes and Barton (2004).
[f] McCormick et al. (1998).
[g] Pickering et al. (1982).
[h] Doyon et al. (2005).
[i] Huising et al. (2004).
[j] Overli et al. (1998).
[k] Doyon et al. (2003).
[l] Overli et al. (2002).

peptide-producing neurons are recruited in the activation of the HPI axis in response to the infection. Moreover, injection of goldfish with the Gram-negative bacteria-derived endotoxin lipopolysaccharide (LPS) elicits a dose-dependent decrease in food intake and an increase in telencephalon, hypothalamus, and olfactory bulb CRF mRNA levels (Volkoff and Peter, 2004). Similarly, in vivo and in vitro LPS treatment in tilapia (*Oreochromis mossambicus*) can modulate brain CRF content and release (Pepels et al., 2004a).

An important pathway for the recruitment of CRF-related peptides during disease-induced anorexia may involve signalling by immune cells to the neuroendocrine system. Infections such as those elicited by LPS stimulate the production of various pro-inflammatory cytokines by peripheral immune cells (Engelsma et al., 2002). Although their effects on the CRF system in fish have not been determined, some of these immune cytokines, such as interleukin-1β, activate the HPI axis in fish (Holland et al., 2002) and stimulate the expression of hypothalamic CRF in mammals (Dunn, 2005).

Given the role of CRF-related peptides as mediators of the appetite-suppressing effects of hypoxia in fish (Bernier and Craig, 2005; see Section 3.1 above), the severe anaemia that characterizes some fish diseases (e.g., Mesa et al., 2000; Olsen et al., 1992; Woo, 2003) may also be a key factor involved in the recruitment of CRF-related peptide-producing neurons during disease-induced anorexia. For example, in fish infected by the protozoan hemoflagellate *Cryptobia salmositica*, the onset of anorexia coincides with a significant rise in parasitemia and severe anaemia (Chin et al., 2004). A metalloprotease produced by the pathogen

lyses circulating erythrocytes (Zuo and Woo, 2000) reducing the oxygen carrying capacity of the infected fish and making them more susceptible to environmental hypoxia (Woo and Wehnert, 1986).

3.3. Physical stressors

Single or repeated physical disturbances such as chasing to exhaustion, handling, or restraint by netting are associated with reductions in food intake in different fish species (McCormick et al., 1998; Pickering et al., 1982). In general, the extent to which feeding is inhibited by physical stressors depends on the severity of the disturbance (Schreck et al., 1997). Similarly, in common carp (*Cyprinid carpio*) and rainbow trout, the intensity and duration of a physical stressor are important factors in determining the magnitude of the changes in CRF gene expression (Doyon et al., 2005; Huising et al., 2004). In carp, while a 30 min restraint period had no effect of hypothalamic CRF mRNA levels, 24 h of restraint was associated with a significant increase in the expression of this transcript (Huising et al., 2004). Similarly, although a single chasing event does not affect CRF mRNA levels in rainbow trout, repeated chasing to exhaustion leads to an increase in preoptic area CRF mRNA levels (Doyon et al., 2005). Overall, while the results from the above studies suggest that appetite-suppressing effects of physical stressors in fish may be associated with an increase in forebrain CRF gene expression, a direct link between CRF-related peptides and the regulation of feeding following physical disturbances remains to be made.

3.4. Social stressors

As evidenced by elevated plasma cortisol and ACTH levels (Hoglund et al., 2000), increased expression of the ACTH precursor pro-opiomelanocortin in the pituitary (Winberg and Lepage, 1998) and CRF mRNA levels in the proptic area (Doyon et al., 2003), social subordination in salmonids is associated with a chronic activation of the HPI axis (see review by Gilmour et al., 2005). Social subordination in these fish is also characterized by a marked reduction in food intake (Winberg et al., 1993). Although dominants can monopolize food, the appetite inhibition in subordinate fish is not merely the result of interference competition from dominants. Instead, the subordination-induced anorexia appears to be mediated by specific brain serotonergic neuronal circuits (Overli et al., 1998). Whether the appetite-inhibitory effects of the serotonergic system in subordinates also involve CRF-related peptide neurons is not known, however, physiological and anatomical evidence suggests interactions between the serotonergic and CRF systems in fish (see Section 4 below). Other social stressors in fish, such as isolation and confinement, have also been associated with increases in preoptic area CRF mRNA levels (Ando et al., 1999; Doyon et al., 2005) and reductions in appetite (Overli et al., 2002). Studies are now needed to establish whether there is a causal relationship between the increase in CRF mRNA levels and the appetite-suppressing effects of these processive stressors.

4. Interaction between CRF-related peptides and other appetite regulators

Both stress-responsive and appetite-regulating neuronal circuits are known to synapse onto CRF-related peptide neurons in mammals (Herman et al., 2003; Itoi et al., 2004; Ueta et al., 2003). Similarly, a variety of different inputs appear to converge on CRF neurons in fish. For example, in tilapia (*Oreochromis mossambicus*) noradrenaline (NA) and serotonin (5-HT) stimulate in vitro CRF release from telencephalic tissues (Pepels et al., 2004a). In goldfish, the CRF receptor antagonist, α-helical $CRF_{(9–41)}$, partially blocks the inhibitory effects of icv 5-HT on food intake (De Pedro et al., 1998), and increased levels of GABA stimulate telencephalic CRF gene expression (Martyniuk et al., 2005). Anatomical evidence also suggests interactions between the stress-responsive serotonergic and noradrenergic cuircuits and the CRF system in fish. Serotonergic cell bodies mainly located in the raphe nuclei but also in cell bodies found in several hypothalamic nuclei contribute fibers to the preoptic region and to the hypothalamic inferior lobe (Frankenhuis-van den Heuvel and Nieuwenhuys, 1984; Meek and Joosten, 1989; Parent, 1983; Terlou et al., 1978). NA-immunoreactive cell bodies located in the locus coeruleus and the brainstem also innervate the preoptic region (Meek, 1994).

Other than correlative evidence between neuropeptide Y (NPY) and CRF gene expression in subordinate rainbow trout (Doyon et al., 2003), the possible involvement of anorexigenic and orexigenic peptidergic inputs in the regulation of the CRF system in fish has not been investigated. In contrast, in the brain of domestic fowl, CRF neurons mediate at least a portion of the anorexigenic effects of pituitary adenylate cyclase-activating polypeptide (PACAP), vasoactive intestinal peptide (VIP), bombesin, and ghrelin (Meade and Denbow, 2003; Saito et al., 2005; Tachibana et al., 2004). Similarly, in rats, NPY (Heinrichs et al., 1993), orexin (Jaszberenyi et al., 2000), prolactin-releasing peptide (PrRP; Lawrence et al., 2004), bombesin (Kent et al., 1998), glucagon-like peptide 1 (GLP-1; Larsen et al., 1997), galanin (Hooi et al., 1990), cocaine- and amphetamine-regulated transcript (CART; Tebbe et al., 2004), and leptin (Okamoto et al., 2001) exert at least a portion of their effects on feeding via interactions with CRF neurons. In contrast, some hypothalamic feeding regulatory factors, for example melanocortins, mediate the appetite-suppressing effects of stressors independently of CRF-related peptides (Vergoni and Bertolini, 2000).

Cortisol, the end product of HPI axis activation in fish (Barton and Iwama, 1991), is also involved in the regulation of food intake. By virtue of its negative feedback effects on forebrain CRF and UI (Bernier et al., 1999; Fryer and Peter, 1977; Olivereau and Olivereau, 1988b), cortisol may counteract the appetite-suppressing effects of CRF-related peptides (Bernier and Peter, 2001b). However, there is also

evidence suggesting that other neuroendocrine pathways mediate the effects of cortisol on food intake. In goldfish, for example, while moderate chronic increases in plasma cortisol stimulate food intake, decrease CRF and increase NPY forebrain expression, larger catabolic doses of cortisol decrease CRF mRNA levels but have no effect on food intake or NPY gene expression (Bernier et al., 2004). Similarly, in rainbow trout, although moderate increases in plasma cortisol over a 6-day period can stimulate self-feeding activity relative to sham-injected fish (Lyytikainen and Ruohonen, 2001), more pronounced elevations in plasma cortisol suppress feed intake (Gregory and Wood, 1999). Chronic catabolic doses of cortisol also decrease feed intake in channel catfish (*Ictalurus punctatus*; Peterson and Small, 2005). Overall, multiple interactions between cortisol and other central and peripheral appetite-regulating signals are likely to contribute to the dose-dependent and complex effects of cortisol on food intake. Finally, while few studies have assessed the specific actions of cortisol on food absorption (Collie and Ferraris, 1995; Collie and Stevens, 1985), the presence of glucocorticoid receptors in the gastrointestinal tract of fish (Ducouret et al., 1995), the stimulatory effects of cortisol on intestinal Na^+–K^+-ATPase activity (Veillette and Young, 2005), and the negative effects of cortisol on circulating triiodothyronine (T3) levels (Brown et al., 1991), all suggest that glucocorticoids may directly or indirectly affect appetite through actions on intestinal nutrient uptake.

5. Concluding remarks

Compelling evidence for a role of CRF-related peptides in the regulation of appetite in fish comes from the demonstration that icv injections of CRF and UI are potent anorexigenic signals and from the observation that CRF receptor antagonists can reverse the appetite-suppressing effects of specific stressors (Bernier and Craig, 2005; Bernier and Peter, 2001b). However, given the stimulatory actions of icv CRF on locomotor activity (Clements et al., 2002; Lowry et al., 1996), it is also possible that at least a portion of the anorexigenic effects of CRF-related peptides are due to behavioural responses that are not mediated through the hypothalamic feeding center. Therefore, to further support the physiological relevance of CRF-related peptides in the regulation of appetite in fish, experiments are needed to determine whether CRF receptor antagonists can modulate the orexigenic or anorexigenic effects of other appetitive neuropeptides.

Similarly, research is needed to determine whether central or peripheral CRF-related peptides mediate some of the appetite-suppressing effects of stressors in fish via actions on the gastrointestinal system. Finally, an understanding of the specific contributions of CRF-R1, CRF-R2, CRF-BP, and of the novel urocortin-related peptides to feeding control is also needed before the true functional significance of the CRF system in the regulation of appetite in fish can be determined.

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