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Review

The hypothalamic–pituitary–interrenal axis and the control of food intake in teleost fish

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Abstract

Although environmental, social and physical stressors have been shown to inhibit food intake and feeding behavior in fish, little is known about the mechanisms that mediate the appetite-suppressing effects of stress. Since the hypothalamic–pituitary–interrenal (HPI) axis is activated in response to most forms of stress in fish, components of this axis may be involved in mediating the food intake reductions elicited by stress. Recent investigations into the brain regulation of food intake in fish have identified several signals with orexigenic and anorexigenic properties. Among these appetite-regulating signals are related neuropeptides that can activate the HPI axis, namely corticotropin-releasing factor (CRF) and urotensin I (UI). Central injections of CRF or UI, or treatments that result in an increase in hypothalamic CRF and UI gene expression, can elicit dose-dependent decreases in food intake that can be reversed by pre-treatment with a CRF-receptor antagonist. Evidence also suggests that cortisol, the end product of HPI activation in most fishes (i.e. Osteichthyes), may be involved in the regulation of food intake. Overall, while elements of the HPI axis may mediate some of the appetite-suppressing effects of stress, it is undetermined how either CRF-related peptides, cortisol, or other elements of the stress response interact with the complex circuitry of the hypothalamic feeding center.

Keywords: Fish; Stress; Appetite; Hypothalamic feeding center; Corticotropin-releasing factor; Urotensin I; Cortisol; Negative feedback regulation

1. Introduction

As the cost of food is one of the major expenditures of intensive fish farming, fish culturists need to be aware of stressful rearing or environmental conditions that inhibit food intake and curtail growth. However, despite an appreciation for the negative impact of stress on food intake, our knowledge of the neuroendocrine mechanisms responsible for the appetite-suppressing effects of stress in fish is superficial at best. In part, this gap in our knowledge is a result of our limited understanding of how the regulation of food intake in fish is achieved and how the stress-sensitive brain circuitry and the hypothalamic–pituitary–interrenal (HPI) axis interact with the control of appetite. Therefore, the aim of this paper is to examine the recent advances in our understand-

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ing of the potential interactions between the mediators of the stress response and the control of food intake in teleost fish (Osteichthyes), and to point out the gaps in our knowledge with the hope of stimulating future research.

2. Food intake, stress and the hypothalamic–pituitary–interrenal axis

Food intake regulation in mammals is achieved via a complex hypothalamic neuronal network that integrates central and peripheral short-term signals of appetite and satiation with long-term signals of energy balance (Kalra et al., 1999). Similarly, available evidence suggests that the regulation of food intake in fish is mediated by a neuronal circuitry of hypothalamic origin that integrates orexigenic and anorexigenic signals (Lin et al., 2000). Within the brain, there is now evidence that neuropeptide Y (NPY), orexins, galanin and β-endorphin may stimulate food intake in fish, whereas CRF-related peptides, serotonin, bombesin, cholecystokinin (CCK), tachykinins and cocaine- and amphetamine-regulated transcript (CART) may be involved in satiation (Lin et al., 2000 and references therein). There is also some indication that insulin (Silverstein et al., 1999; Silverstein and Plisetskaya, 2000), growth hormone, CCK (Lin et al., 2000) and cortisol (Gregory and Wood, 1999) may behave as peripheral feedback signals that are integrated by the hypothalamic feeding center. Currently, the evidence for a potential involvement of leptin in the regulation of fish appetite, adiposity and metabolism is equivocal (Baker et al., 2000; Johnson et al., 2000; Silverstein and Plisetskaya, 2000). Overall, beyond the identification of the above factors as potential signals of appetite and satiation, relatively little is known about the precise mechanisms responsible for the control of food intake in fish (Lin et al., 2000).

A characteristic behavioral response to stress in fish appears to be a reduction in food intake (Schreck et al., 1997; Wendelaar Bonga, 1997). In fact, in addition to its appetite-suppressing effects, stress can disrupt many other aspects of the feeding behavior in fish. For example, food searching, finding, or capturing can all be affected by stress (Beitinger, 1990). Furthermore, several different types of stress, including environmental (low pH, high ammonia, low dissolved oxygen and pollutants), social (subordination and crowding), or physical (handling) challenges, have all been shown to inhibit food consumption in fish (Schreck et al., 1997; Wendelaar Bonga, 1997). All in all, the varied effects of stress on feeding behavior, and the broad range of stressors that can suppress feeding, suggest that the interactions between the pathways mediating the stress response and the regulation of food intake in fish are likely to be complex.

A general feature of the primary stress response in fish is an activation of the HPI axis (Wendelaar Bonga, 1997). Upon stimulation by stress, neurosecretory neurons originating in the hypothalamic nucleus preopticus (NPO) and nucleus lateral tuberalis (NLT) release neuropeptides with adrenocorticotropin hormone (ACTH) releasing activities in the pituitary (Lederis et al., 1994). Among these neuropeptipes, in vitro evidence suggests that the related neuropeptides CRF and UI have the highest intrinsic ability to stimulate ACTH, and UI may have the highest potency (Lederis et al., 1994). In vivo, although there is some evidence implicating the CRF neurons of the NPO as potential mediators of the stress response in fish (Ando et al., 1999; Bernier et al., 1999), the specific pathways and neuropeptides that control the secretion of ACTH in response to individual stressors have not been identified. In contrast, subordination stress, handling and predator exposure are known to elevate brain serotonin activity in teleost species (Winberg and Nilsson, 1993), and hypothalamic serotonin appears to play an important role in HPI axis regulation (Winberg et al., 1997; Winberg and Lepage, 1998). While in mammals serotonin can activate the HPI axis by directly stimulating the release of CRF from hypophysiotropic neurons and ACTH from the pituitary (Dinan, 1996), the level at which serotonin exerts its effects on the HPI axis in fish is not known (Winberg et al., 1997). Overall, various stressors elicit the secretion of ACTH from the pituitary of fish, and an increase in circulating ACTH is the primary signal that drives the synthesis and secretion of cortisol from the interrenal cells of the teleost head kidney (Wendelaar Bonga, 1997). Most forms of stress appear to result in an elevation of plasma cortisol (Barton and Iwama, 1991), and cortisol exerts a negative feedback action on ACTH secretion from the pituitary (Fryer et al., 1984) and CRF and UI synthesis in the hypothalamus (Bernier et al.,

1999; Bernier and Peter, 2001). Therefore, given that activation of the HPI axis is at the center of the stress response in fish, components of the HPI axis are likely to play an important role in mediating a stress-elicited reduction in food intake.

3. Corticotropin-releasing-factor, urotensin I and food intake

In fish, as in mammals (Heinrichs and Richard, 1999), CRF-related neuropeptides are potent anorexigenic signals. In goldfish, *Carassius auratus*, intracerebroventricular (icv) administration of either ovine CRF (De Pedro et al., 1993), rat/human CRF, or carp/goldfish UI (Bernier and Peter, 2001) inhibits food intake in a dose-related manner. The anorectic effects of CRF-related peptides in goldfish can be reversed by pre-treatment with the CRF receptor antagonist, α-helical $CRF_{(9-41)}$ (De Pedro et al., 1997; Bernier and Peter, 2001). Although central injections of CRF and UI can also elicit an increase in plasma cortisol levels in goldfish, the anorectic effects of CRF and UI in fish appear to be independent of an activation of the HPI axis and mediated through central mechanisms involving CRF receptors (De Pedro et al., 1997; Bernier and Peter, 2001). Overall, icv UI is significantly more potent than icv CRF at suppressing food intake in goldfish (Bernier and Peter, 2001). Similarly, the mammalian equivalent to UI, urocortin, appears to be more potent than CRF in suppressing appetite in rats (Spina et al., 1996). While the functional significance of the differential ability of CRF and UI to inhibit food intake in fish remains to be investigated, there are physiological differences in the way that CRF and urocortin promote reductions in food intake in mammals (Heinrichs and Richard, 1999).

In order to investigate how an increase in the activity of the CRF and UI-synthesizing neurons of the brain may affect the ingestive behavior of fish, we recently assessed the impact of pharmacologically removing the negative feedback action of cortisol on food intake in goldfish (Bernier and Peter, 2001). Goldfish given intraperitoneal (ip) implants of the glucocorticoid receptor antagonist, RU-486, or the cortisol synthesis inhibitor, metyrapone, were characterized by a sustained and dose-dependent reduction in food intake. In a parallel experiment, we observed that ip administration of RU-486 and metyrapone both led to a chronic increase in CRF and UI gene expression in the telencephalon–preoptic and hypothalamic brain regions of the goldfish brain, respectively. As indicated by their effects on the circulating levels of plasma cortisol, the implants of RU-486 and metyrapone stimulated the activity of CRF and UI-synthesizing neurons via different modes of action (Bernier and Peter, 2001). Whereas metyrapone blocked the negative glucocorticoid feedback mechanism by inhibiting cortisol synthesis, RU-486 treatment led to a temporary cortisol hypersecretion by counteracting the negative feedback action of cortisol on the HPI axis (Bernier et al., 1999). Finally, icv pre-treatment with implants of the CRF receptor antagonist, α-helical $CRF_{(9-41)}$, partially reversed the appetite-suppressing effects of RU-486 and metyrapone treatments. Together, these results suggest that endogenous CRF-related peptides may play a physiological role in the control of food intake in fish.

Investigations into the interactions of CRF with other anorexigenic and orexigenic systems suggest that CRF-related peptides may be involved in a wide variety of appetite-regulating pathways. For example, in mammals CRF inhibits feeding induced by NPY, and mediates at least a portion of the anorexigenic effects of bombesin, leptin and possibly serotonin (Bovetto et al., 1996; Kent et al., 1998; Heinrichs and Richard, 1999). Similarly, the ability of α-helical $CRF_{(9-41)}$ pre-treatment to partially prevent the appetite-suppressing effect of icv serotonin in goldfish (De Pedro et al., 1998b) suggests that CRF may mediate part of the anorectic effects of brain serotonin in fish. Since socially subordinate fish are characterized by suppressed feeding, an enhanced brain serotonergic activity, and an elevation in plasma ACTH and cortisol levels (Winberg et al., 1993; Höglund et al., 2000), it is possible that CRF-related peptides are involved in mediating the appetite-suppressing effects of subordination stress in fish. Given the complexity of the pathways regulating appetite, establishing the involvement of CRF or UI in mediating the anorectic effects of subordination stress is just one example of the many future challenges facing physiologists as they try to determine how specific stressors affect the feeding behavior of fish.

4. Plasma cortisol and food intake

Although it is widely accepted that cortisol is a primary mediator of the growth-suppressing effects of stress (Pickering, 1993; Pankhurst and Van der Kraak, 1997), surprisingly little information exists on the physiological role of cortisol in the regulation of food intake in fish. Since elevated plasma cortisol levels is a hallmark of the stress response in fish (Barton and Iwama, 1991), it seems reasonable to assume that a likely mechanism underlying the appetite suppressing effects of stress in fish may be an increase in plasma cortisol (Beitinger, 1990). However, while the catabolic properties of cortisol in fish are well recognized (Mommsen et al., 1999), most studies investigating the growth suppressing effects of cortisol in fish have not specifically assessed the impact of cortisol on food intake (e.g. Davis et al., 1985; Barton et al., 1987; Van Weerd and Komen, 1998). In support of an appetite-suppressing effect of cortisol in fish, a recent study observed that rainbow trout, *Oncorhynchus mykiss*, exhibiting chronic elevations in plasma cortisol levels had significantly depressed food intake (Gregory and Wood, 1999). However, interpretation of the results from the study of Gregory and Wood (1999) is complicated by the fact that the cortisol-treated fish appeared to exhibit aggression towards each other and experienced a significant level of mortality. In contrast, ip injections of cortisol have no acute affects on food intake in goldfish (De Pedro et al., 1997; Bernier and Peter, unpublished observation). Moreover, although daily acute stress chronically reduced the food consumption of Atlantic salmon parr, *Salmo salar*, plasma cortisol levels in the stressed group were significantly lower than in controls after 42 days of treatment (McCormick et al., 1998).

Even though some of the mechanisms of action and physiological roles of cortisol in fish differ from those observed in mammals (Mommsen et al., 1999), insight into the potential role of cortisol in the regulation of food intake in fish may be gained from an understanding of the extensive mammalian literature on this topic. Overall, glucocorticoids within the physiological range are potent orexigenic signals in mammals that stimulate appetite slowly over days (Sapolsky et al., 2000). In fact, glucocorticoid secretion from the adrenal cortex is essential for the development of all forms of obesity in rodents (Bray and York, 1998). Glucocorticoids are thought to stimulate food intake in part by reversing the inhibitory effects of leptin and insulin on food intake, by stimulating central NPY synthesis, and by inhibiting hypothalamic CRF production (Woods et al., 1998). On the other hand, large catabolic doses of glucocorticoids can inhibit food intake by stimulating leptin production and by eliciting an increase in plasma insulin levels (Michel and Cabanac, 1999; Sapolsky et al., 2000). Finally, mineralocorticoid and glucocorticoid receptor types mediate distinct effects of glucocorticoids in the regulation of nutrient intake (Tempel and Leibowitz, 1994). Thus, the mechanisms of glucocorticoid effects on food intake regulation in mammals are complex, dose-dependent and influenced by nutritional status.

5. Future considerations

Elucidating how mediators of the stress response in fish interact with the neuronal network of the hypothalamic feeding center, and the peripheral signals of appetite and satiation, represents a considerable challenge. Among the tasks ahead is a precise identification of the CRF and UI neurons involved in the control of food intake. Since the anorectic actions of CRF-related peptides may be independent of the HPI axis, the anatomical origin of the CRF and UI neurons involved in appetite regulation may differ from the hypophysiotropic neurons of the NPO and the NLT. While considerable evidence suggests that a CRF-binding protein is implicated in the regulation of appetite in mammals (Heinrichs and Richard, 1999), a fish homologue remains to be identified. In addition to their appetite-suppressing effects, central administration of CRF-related peptides in mammals can elicit a number of behavioral and autonomic responses that contribute to a reduction in feeding behavior (Heinrichs and Richard, 1999). Similar investigations are required to determine the physiological relevance of central CRF-related peptides as anorexigenic agents in fish. While this review focused on the HPI axis, the regulation of food intake by other central and peripheral mediators of the stress response, e.g. serotonin (Winberg and Nilsson, 1993) and catecholamines (De Pedro et al., 1997, 1998a), will also have to be taken into considera-

tion. Finally, significant advances will also come from the molecular and pharmacological characterization of the glucocorticoid, mineralocorticoid, and CRF receptors of fish (Darlison et al., 1997; Teitsma et al., 1997; Colombe et al., 2000), and from the localization of these receptors in the neuronal network of the hypothalamic feeding center.

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