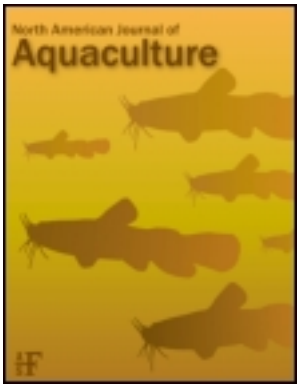

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[Article]

Elucidating the Effects of Cortisol and Stress on Economically Important Traits in Channel Catfish

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Abstract.—The channel catfish *Ictalurus punctatus* is an important aquaculture species in the United States and has received considerable research attention in efforts to improve production. Three traits of importance to the U.S. farm-raised channel catfish industry are disease resistance, growth, and reproduction. While many factors affect these three traits, a fish's response to stress can have a substantial impact on production attributes. Understanding the relationships between the stress response and components of that response, such as plasma cortisol concentration, is important to the development of better management and breeding practices to maximize production. Although much of the data regarding the fish physiological consequences of stress and elevated plasma cortisol has been collected from studies of salmonids, recent advances have been made toward understanding these relationships in channel catfish. The present review synthesizes the research conducted over the past several years regarding the effects of stress and cortisol on disease susceptibility, growth, metabolism, and reproduction of channel catfish in the context of how stress and cortisol affect economically important production traits for aquaculture.

Channel catfish *Ictalurus punctatus* lead U.S. aquaculture food fish production, contributing over 272 million kilograms in annual production valued at approximately US$450 million (USDA 2006, 2007). The importance of this species to the U.S. aquaculture industry has resulted in substantial research efforts to improve germplasm and production practices. Three traits of economic importance that have received much attention are disease resistance, growth, and reproduction; however, many factors, including environmental, genetic, and social influences, can significantly impact the expression of superior phenotypes for these traits.

Channel catfish production conditions and practices, like those common to other aquaculture ventures, can result in stressful conditions that alter the physiology of the fish. Conditions such as handling (Davis et al. 1993), poor water quality (Tomasso et al. 1981a, 1981b; Small 2004b), and exposure to toxins (Griffin et al. 1999; Schlenk et al. 1999) have been shown to induce a channel catfish stress response that is characterized by physiological changes typifying the known stress response of teleost fish. While there is no wholly agreed upon definition of stress, it is interesting to note that many different scientific disciplines accept the concept of stress. Wendelaar Bonga (1997) suggested that the widespread acceptance of the stress concept demonstrates the attractiveness of describing very different phenomena observed at many levels of organization (i.e., cells, organs, organisms, populations, and ecosystems) on the basis of a unifying concept. In his review, Wendelaar Bonga (1997) defined stress as a condition that disturbs or threatens the homeostasis of an organism as a result of the actions of intrinsic or extrinsic stimuli, or stressors. A more simplistic definition that is widely accepted is that stress is simply the nonspecific response of the body to any demand made upon it (Selye 1973).

For convenience, stress responses have been categorized as primary, secondary, and tertiary according to the level of organization of the response. Primary responses include elevations in plasma catecholamine, corticosteroids, and adrenal corticotrophin hormone. Secondary responses include changes in many metabolic (i.e., plasma glucose), hematological (i.e., hematocrit), hydromineral (i.e., chloride), and structural (i.e., interrenal cell size) features. Whole-animal responses, such as changes in growth, metabolic rate, and disease resistance, are representative of tertiary responses to stress. In teleost fish, cortisol is considered the principal corticosteroid, and circulating concentrations of cortisol increase rapidly after the perception of stress. As a result, plasma cortisol is one of the most commonly measured indicators of stress. Cortisol has been shown to play important roles in intermediary metabolism, growth, ionic and osmotic regulation, reproduction, and immune function. (Wendelaar Bonga 1997; Mommsen et al. 1999). Undoubtedly, the growing evidence supporting the importance of cortisol in maintaining homeostasis, together with the ease of measuring cortisol and the magnitude of cortisol

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TABLE 1.—Summary of representative studies reporting changes in channel catfish plasma cortisol concentration (ng/mL) resulting from experimentally administered stressors or exogenous cortisol administered in feed (mg of cortisol/kg of feed). Poststress values are reported with sampling time (in parentheses). Some cortisol values were estimated from graphs.

Stressor and experimental conditions	Prestress cortisol	Poststress cortisol	Source
Continuous net confinement at			
5°C	29	55 (6 h)	Davis et al. (1984)
10°C	25	30 (6 h)	Davis et al. (1984)
15°C	5	55 (6 h)	Davis et al. (1984)
20°C	8	60 (6 h)	Davis et al. (1984)
25°C	12	95 (6 h)	Davis et al. (1984)
30°C	13	95 (6 h)	Davis et al. (1984)
35°C	12	95 (6 h)	Davis et al. (1984)
2-h transport	4	132 (2 h)	Davis and Parker (1986)
Continuous low-water confinement	15	65 (2 h)	Davis et al. (2002)
Continuous low-water confinement	15	25 (6 h)	Davis et al. (2002)
Continuous basket confinement	31	103 (30 min)	Sink and Strange (2004)
Continuous fasting	5	23 (30 d)	Peterson and Small (2004)
Continuous basket confinement	31	110 (60 min)	Sink and Strange (2004)
Continuous crowding	8	53 (15 min)	Small (2004b)
Continuous crowding	8	53 (30 min)	Small (2004b)
Continuous crowding	8	53 (45 min)	Small (2004b)
Continuous exposure to 1-mg/L un-ionized ammonia	7	34 (24 h)	Small (2004b)
Continuous exposure to <0.5-mg/L dissolved oxygen	6	55 (30 min)	Small (2004b)
30-min static challenge with *Edwardsiella ictaluri*	7	31 (2 d)	Bilodeau et al. (2005)
Continuous low-water confinement	2	31 (30 min)	Karsi et al. (2005)
Continuous low-water confinement	2	24 (1 h)	Karsi et al. (2005)
Cortisol in feed at 200 mg/kg, 1% of body weight	13	118 (6 h)	Davis et al. (2003)
Cortisol in feed at 200 mg/kg to satiation	3	180 (4 h)	Peterson and Small (2005)
Cortisol in feed at 400 mg/kg to satiation	3	520 (4 h)	Peterson and Small (2005)
Cortisol in feed at 100 mg/kg to satiation	4	103 (4 h)	Small and Bilodeau (2005)

response to stress, makes it a convenient measure and the predominantly reported stress indicator.

A majority of fish studies demonstrate the direct association of cortisol with observed physiological changes during stress based almost solely on plasma cortisol concentrations. Inconsistencies in the literature regarding the action of cortisol secreted during stress or when administered exogenously suggest that such reliance on one indicator to explain the effects of stress are inadequate and impede a thorough understanding of the stress response in fish (Mommsen et al. 1999). An underlying assumption of many studies is that elevated concentrations of cortisol in circulation are deleterious to the fish; however, direct assessments of cortisol actions separate from or even associated with stress are often inconclusive. Barton and Iwama (1991) stated that direct cause–effect relationships attributed to cortisol during stress had yet to be established. Arguably, progress toward establishing those relationships has continued to be slow.

The objective of this review is to synthesize the research conducted over the past several years regarding the effects of stress and cortisol on disease susceptibility, growth, metabolism, and reproduction of channel catfish in the context of how stress and cortisol affect economically important production traits for aquaculture. In this, we hope to stimulate thought and discussion regarding the importance of the stress response and cortisol with regard to improving the production of all aquaculture species.

Plasma Cortisol Concentrations

Over the past two decades, much research has focused on the effects of aquaculture-related stressors on channel catfish physiology and performance. The types of experiments conducted have varied considerably, as have the reported concentrations of pre- and poststress plasma cortisol (Table 1). Differences in prestress concentrations are often the result of the experimental protocol used and therefore may not reflect actual resting levels. Genetic, developmental, and environmental history may also impact these values, as indicated by the vast diversity of cortisol stress responses reported for various fishes (reviewed by Barton 2002). Resting plasma cortisol concentrations for channel catfish are generally thought to be less than 10 ng/mL and were reportedly less than 2.5 ng/mL when metomidate was used to block cortisol release in nonstressed channel catfish (Small 2003; Davis and Small 2006). Differences in poststress concentrations probably reflect differences in the severity of stress but may also reflect genetics, environment, and life stage. Too often, the genetic or environmental history is not documented, making proper interpretation difficult.

Generally, channel catfish plasma cortisol concentrations measured after application of a physical stressor are in the range of 50–140 ng/mL (Table 1). Some earlier reports with channel catfish documented corticosteroid levels after confinement to be as high as 225 (Strange 1980) and 309 ng/mL (Ainsworth et al. 1985); however, concentrations above 200 ng/mL are atypical for this species.

Stress-induced elevations in plasma cortisol have been mimicked in channel catfish through the administration of exogenous cortisol via the diet (Davis et al. 1985; Small 2004a; Peterson and Small 2005; Small and Bilodeau 2005; Small et al. 2006). This methodology provides a means of chronically elevating plasma cortisol and also allows for the actions of cortisol to be assessed without application of a stressor to the fish. In this regard, it can be used to evaluate the inherent role of cortisol in channel catfish physiology. Because of the complexity of the stress response, the administration of exogenous cortisol is probably not a good model for stress. Several levels of dietary cortisol inclusion have been used in channel catfish, ranging from 50 to 400 mg of cortisol/kg of feed. Diet concentration and feeding rate affect peak plasma concentrations (Table 1); however, peak levels consistently have been reported to occur between 4 and 6 h after feeding, and prefeeding levels are not reached until 12–24 h later.

Disease Susceptibility

The effects of stress on disease susceptibility in fish have received a great deal of attention. Each year, it is estimated that hundreds of thousands of channel catfish produced in the USA are lost due to disease outbreaks. While this may appear exceptional, disease is considered the single greatest cause of reduced productivity in most aquaculture production systems. Historically, the stressors associated with intensive fish culture have been considered to exacerbate disease susceptibility (Snieszko 1974; Wedemeyer 1974; Mazeaud et al. 1977; Maule et al. 1989). Early studies of salmonids linked stress induced by aquaculture practices to increases in circulating cortisol concentrations and suggested that cortisol in turn suppressed the immune system, thus rendering these fish more susceptible to disease. Those studies demonstrated that fish subjected to handling stressors or poor water quality had a reduced ability to resist pathogens (Wedemeyer 1974; Schreck et al. 1985; Maule et al. 1989). Furthermore, cortisol-implanted salmonids were found to be more susceptible to pathogens (Pickering and Duston 1983) and to exhibit immunosuppression (Maule et al. 1987).

More recent studies have also demonstrated negative effects of handling, crowding, social stressors, and behavioral stressors on fish health and immune function (Barton and Iwama 1991; Schreck 1996; Wendelaar Bonga 1997) and have shown that prolonged elevations of plasma cortisol associated with chronic stress are detrimental to immune function. In some cases, however, responses to acute stress events have been observed to enhance immunity and positively alter hematology (Peters and Schwarzer 1985; Möck and Peters 1990; Peters et al. 1991; Dhabhar et al. 1996; Demers and Bayne 1997). It was suggested by Demers and Bayne (1997) that such observations are associated with the fight-or-flight response that prepares an organism for coping with alarming situations, such as pathogen exposure. In their research, Demers and Bayne (1997) observed a short-term enhancement in lysozyme (a plasma protein that is central to innate defenses) activity after acute stress in rainbow trout *Oncorhynchus mykiss*, suggesting that the well-established long-term immunosuppressive effects of stress are preceded by short-term immune system enhancement. Furthermore, it has been demonstrated that cortisol causes the redistribution of components of the innate immune system to peripheral sites where they can present a front line of defense. This again is contrary to the maladaptive consequences of downregulation of acquired immunity observed during chronic stress (Schreck and Maule 2001).

In an effort to address the apparent paradoxes in the literature for other species of cultured fishes regarding immunomodulation during acute stress and exogenous cortisol administration, several studies have been conducted with channel catfish over the past few years (Table 2). In each of those studies, fish were subjected to either an acute handling stress or exogenous cortisol administration. Generally, the fish were exposed to an acute confinement stressor by physical crowding or a lowering of the water volume. Exogenous cortisol in the respective studies was administered orally by incorporating cortisol into commercial channel catfish feeds.

Early reports on the effects of stress on channel catfish disease susceptibility demonstrated substantial negative effects, such as increased susceptibility to infection by the bacteria *Aeromonas hydrophila* (Walters and Plumb 1980) and *Edwardsiella ictaluri* (Wise et al. 1993). Walters and Plumb (1980) observed that channel catfish subjected to stress via various combinations of low dissolved oxygen, high carbon dioxide, and high ammonia resulted in a predisposition to bacterial infection. Not only did the stressed fish have a 56% higher incidence of *A. hydrophila* infection than nonstressed fish, but *Edwardsiella tarda* (apparently endemic to the population) was also isolated from 43% of the stressed fish and only 7% of the nonstressed

TABLE 2.—Results of studies describing the effects of acute stress (e.g., handling or confinement) and exogenous cortisol (i.e., administered in feed) on increasing (↑) or decreasing (↓) pathogen susceptibility and associated mortality in channel catfish challenged with a pathogen (bacteria, parasite, or virus) relative to pathogen-infected control fish (N/A = not applicable to the studies referenced; ND = no difference).

Pathogen	Difference in: Infection rate (%)	Difference in: Cumulative mortality (%)	Source
Acute stress			
Edwardsiella ictaluri[a]	N/A	27% ↑	Wise et al. (1993)
	N/A	25–74%	Sink and Strange (2004)
	10% ↑	17 ↑	Small and Bilodeau (2005)
Aeromonas hydrophila	56 ↑	17–71 ↑	Walters and Plumb (1980)
Ichthyophthirius multifiliis[b]	18–28 ↑	N/A	Davis et al. (2002)
Channel catfish virus	ND	ND	Davis et al. (2002)
Exogenous cortisol			
E. ictaluri	ND	ND	Small and Bilodeau (2005)
I. multifiliis	ND to 2 ↑	N/A	Davis et al. (2003)
Channel catfish virus	ND	ND	Davis et al. (2003)

[a] Agent of enteric septicemia of catfish.
[b] Agent of ich disease.

fish. Lesions were also noted in several tissues of stressed fish but not control fish. Furthermore, the various combinations of stressors resulted in a 19–71% increase in disease-associated mortality.

Enteric septicemia of catfish (ESC), which is caused by the bacterium *E. ictaluri* (Hawke 1979), is the most prevalent disease affecting farm-raised channel catfish in the United States and is responsible for up to 50% of the total losses incurred by channel catfish farmers each year (USDA 1997). The pathology of ESC is well defined (Shotts et al. 1986; Newton et al. 1989; Baldwin and Newton 1993); however, the modulating effects of stress and cortisol on susceptibility of channel catfish to *E. ictaluri* are not so well defined. Wise et al. (1993) examined the effects of acute stress on channel catfish experimentally infected with *E. ictaluri* and reported an approximately 27% higher cumulative mortality in fish subjected to a 30-min confinement stress 1 h before challenge relative to challenged fish that were nonstressed. More recently, Sink and Strange (2004) revisited the effects of stress on susceptibility to *E. ictaluri* by exposing channel catfish to a basket confinement stressor for 30 and 60 min. They too observed a significant increase in mortality (25–74%) in stressed fish infected with the pathogen relative to nonstressed, pathogen-infected fish. In small fingerling channel catfish (70–85 mm), Sink and Strange (2004) reported an increase in mortality with increased duration of stress, which also corresponded to increases in plasma cortisol. In large fingerlings (114–168 mm), the percent of dead fish also increased with increased stress duration; however, elevations in plasma cortisol were similar after both 30 and 60 min of confinement. Small and Bilodeau (2005) examined the effects of stress on susceptibility to *E. ictaluri* by exposing channel catfish to a 30-min low-water stressor 45 min prior to pathogen exposure; they expanded their study to include an exogenous cortisol treatment in which the fish were fed 100 mg/kg to satiation 4 h prior to *E. ictaluri* infection. Their results demonstrated differential effects of acute stress and cortisol on bacterial infection rates, pathogen-associated mortalities, and lysozyme activities. Briefly, pathogen susceptibility in acutely stressed channel catfish increased nearly 17% relative to nonstressed controls. Interestingly, mortality in channel catfish fed exogenous cortisol was the same as that in nonstressed fish and 17% lower than that in stressed fish, even though plasma cortisol levels were significantly elevated in cortisol-fed fish (Table 1). Further, a greater percentage of stressed channel catfish (26%) tested positive for *E. ictaluri* relative to cortisol-fed (13%) and control (16%) fish. Higher lysozyme levels were also reported in stressed fish relative to the other two treatment groups; however, a positive correlation to tissue pathogen levels suggested that the difference in lysozyme activity was a result of increased infection rather than a result of stress-stimulated immune augmentation.

Although bacterial pathogens, particularly *E. ictaluri*, have received the greatest amount of research attention among channel catfish pathogens, Davis et al. (2002, 2003) have investigated whether exogenous cortisol administered in feed prior to parasitic or viral pathogen exposure affects fish susceptibility to two other common channel catfish pathogens, *Ichthyoph-*

thirius multifiliis and channel catfish virus (CCV), in a differential manner relative to fish subjected to acute stress or no stress prior to pathogen exposure. In examining the relationships of stress and cortisol to *I. multifiliis* susceptibility, Davis et al. (2002) observed a moderate increase in trophont infestation when fish were confined for 2 h prior to pathogen exposure. A pronounced increase in trophont infestation was noted when the confinement stress was extended to 6 h. A similar effect was observed when channel catfish were fed exogenous cortisol for 13 d prior to *I. multifiliis* exposure; Davis et al. (2003) observed a modest increase in trophont infestation for fish that were fed 100 mg cortisol/kg feed and a significant increase in trophont infestation for fish that were fed 200 mg cortisol/kg. Plasma cortisol concentration peaked at 118 ng/mL 6 h after feeding in the 200-mg/kg treatment group (Table 1). Mortality associated with *I. multifiliis* was not reported for either study. In those same studies, Davis et al. (2002, 2003) also examined the effects of stress and exogenous cortisol on CCV susceptibility. Regardless of the duration of stress or the concentration of dietary cortisol administered prior to infection, no significant differences in CCV-associated mortality were observed across a wide range of virus exposure rates.

Differences in stressor type and duration, disease challenge protocols, and procedures and (in some cases) a lack of plasma cortisol values for the studies presented in Table 2 hinder direct comparisons of the results. Some trends, however, are apparent. In each study using a bacterial pathogen, infection rates and mortality were higher when acute stress was administered to channel catfish prior to pathogen exposure. The lack of stress effects on CCV mortality was suggested by Davis et al. (2002) to result from either (1) protection afforded by an inducible system that was not affected by stress or (2) the lethal effects of CCV being too fast for the stress to change susceptibility in native fish. Both possibilities are merely speculative at this time. As for fish fed cortisol, uptake profiles in the various studies demonstrated that elevated plasma cortisol levels were within physiological expectations for a stressed fish. Nonetheless, exogenous cortisol without an induced stress response appears to have little or no effect on disease susceptibility for any of the pathogens studied. Channel catfish fed cortisol at 200 mg/kg (total ration of 3% of body weight) for 13 d prior to *I. multifiliis* exposure had approximately 2% higher trophont infestation, which was statistically significant but may not be biologically significant. Taken together, these studies suggest that acute stressors lower the ability of channel catfish to resist pathogens (CCV being the exception); however, cortisol alone does not appear to be the causative agent in the cascade of the fish stress response.

Growth and Metabolism

Stress is generally considered to inhibit somatic growth through increased or modified metabolic expenditures. Anybody who has raised fish can provide a plethora of anecdotal evidence that demonstrates reduce growth in stressed fish. Although several experiments have been conducted in an effort to establish the physiological relationships between stress and fish growth, many have yielded ambiguous results (reviewed by Van Weerd and Komen 1998). A reduction or cessation of feed intake is one very observable and often-reported result of physical, environmental, and disease stressors on fish behavior that undoubtedly contributes to decreased growth (Andrews et al. 1973; Macket et al. 1992; Peterson and Brown-Peterson 1992; Hoskonen and Pirhonen 2006). Environmental stressors have been reported to reduce feed intake, weight gain, and conversion efficiency in channel catfish (Andrews et al. 1973; Peterson and Brown-Peterson 1992). In addition to reduced weight gain, Peterson and Brown-Peterson (1992) observed reductions in RNA concentration, RNA : DNA ratios and protein : DNA ratios in hypoxia-stressed channel catfish, suggesting reductions in protein synthesis and relative cell mass. Plasma cortisol levels are also reportedly elevated in oxygen-deprived channel catfish (Tomasso et al. 1981a; Small 2004b). Other reported effects of stress on growth-related parameters in fish include reduced nutrient absorption (Barton et al. 1987; Peters 1982), increased protein turnover (Houlihan et al. 1994), and altered concentrations of circulating growth factors, including growth hormone (GH) and insulin-like growth factors (IGF-I and IGF-II; Pickering et al. 1991; Auperin et al. 1997; McCormick et al. 1998; Wilkinson et al. 2006).

The effects of chronic stress on growth and metabolism are generally accepted to be mediated through the actions of cortisol. As such, exogenous cortisol administration has been used as a model to simulate the effects of chronic stress in fish. Studies demonstrating reduced growth in fish that were administered cortisol date back to the late 1960s, when Storer (1967) demonstrated that injected cortisol decreased body weight in fed goldfish *Carassius auratus* and further increased weight loss in starved goldfish. The downregulation of fish growth during periods of stress has since been directly linked to the hypothalamic–pituitary–interrenal (HPI) axis (Pickering 1990, 1992; Van der Boon et al. 1991; Vijayan et al. 1996). Metabolic changes due to cortisol have been summarized by Van Weerd and Komen (1998)

TABLE 3.—Summary of growth- and metabolism-associated responses in channel catfish after exogenous cortisol administration (i.e., in feed).

Decreased response	Increased response
Growth[a–d]	Plasma glucose[b]
Condition factor[a]	Tyrosine aminotransferase[a,e]
Feed intake[c]	Plasma 20-kDa IGF-binding proteins[c]
Feed efficiency[a,c]	Pituitary growth hormone mRNA[c]
Hepatosomatic index[a,b]	
Liposomatic index[a]	
Liver growth hormone receptor messenger RNA (mRNA)[d]	
Plasma insulin-like growth factor (IGF)-I[c,d]	

[a] Davis et al. (1985).
[b] Small (2004a).
[c] Peterson and Small (2005).
[d] Small et al. (2006).
[e] Enzyme number 2.6.1.5 (IUBMB 1992).

and Mommsen et al. (1999) and demonstrate that glucose production and hepatocyte metabolism are directly affected by cortisol.

The effect of exogenous cortisol administration on channel catfish growth and metabolic changes was first examined by Davis et al. (1985; Table 3). In their study, cortisol was incorporated into the diet at varied concentrations and the feed was offered to juvenile channel catfish at 3% of body weight per day for 10 weeks. When fish were given 100 mg cortisol/kg feed, they exhibited significant reductions in body weight, condition factor, feed efficiency, hepatosomatic index, and liposomatic index. Small (2004a) also observed reduced somatic and liver weight when feeding cortisol to channel catfish broodstock. Furthermore, Davis et al. (1985) reported that the specific activity of hepatic tyrosine aminotransferase (TAT) substantially increased in fish given cortisol in feed at concentrations of 50 and 100 mg/kg. Tyrosine is a ketogenic and gluconeogenic amino acid that is convertible to both acetoacyl-CoA and fumarate, and TAT is the rate-limiting step. Davis et al. (1985) suggested that the observed inverse relationship of TAT activity with growth rate and lipid store in cortisol-fed fish provides a physiological explanation of decreased food efficiency and growth. Their results suggest that cortisol released into circulation during stress retards channel catfish growth by promoting protein catabolism, lipolysis, and inefficient feed conversion.

The GH–IGF (somatotropic) axis plays an integral role in animal growth. The actions of factors involved in this axis are conserved in fish (Moriyama et al. 2000) and may well be modulated by cortisol in channel catfish, as has been demonstrated in other teleost species (Pickering et al. 1991; Auperin et al. 1997; McCormick et al. 1998; Wilkinson et al. 2006). In an effort to elucidate interactions between cortisol and the GH–IGF axis as related to channel catfish growth, Peterson and Small (2005) administered cortisol to juveniles at 200 and 400 mg/kg in feed once daily to satiety for 4 weeks (Table 3). While the 200-mg/kg treatment resulted in maximum circulating cortisol levels at the high end of normal physiological concentrations during a severe stress event, the 400-mg/kg treatment fish had pharmacological concentrations of cortisol in the plasma (Table 1). Their results clearly demonstrated reduced somatic growth in both cortisol treatment groups (16–18% of control growth) and decreased feed intake (26–40% of control intake). Interestingly, no effect of cortisol on pituitary GH messenger RNA expression was noted in the 200-mg/kg treatment group; however, pharmacological levels of plasma cortisol observed in 400-mg/kg treatment fish resulted in a nearly 10-fold increase in GH expression. Further, IGF-I levels in the plasma were significantly reduced (nearly threefold) in channel catfish receiving cortisol, but no differences were observed in hepatic IGF-I mRNA expression. Peterson and Small (2005) also reported changes in plasma IGF-binding proteins (IGFBPs) in channel catfish fed cortisol at both dietary concentrations. An approximately 20-kilodalton (kDa) IGFBP that was not present in control fish was induced in the cortisol-treated fish. Also, IGFBPs of approximately 35 and 45 kDa were also detected in the plasma of all fish in the study, and no differences in expression were apparent between treatments. The authors suggested that one mechanism by which cortisol acts to impede growth is IGFBP modulation that in turn regulates the growth-promoting effects of IGF-I.

The effects of cortisol on channel catfish GH and IGF-I expression reported by Peterson and Small (2005) are similar to those observed in fasted channel catfish (Peterson and Small 2004). When fish were fasted for 30 d, increased levels of cortisol (Table 1) and a 20-kDa IGFBP were reported in conjunction with

retarded growth, poor condition factor, and reduced liver weight. Taken together, these two studies suggest that cortisol plays an important role in the regulation of the GH–IGF axis during fasting as well as during application of other stressors. Further evidence for this relationship was presented by Small et al. (2006). They gave channel catfish cortisol in feed at a rate of 200 mg/kg for 4 weeks and compared its effects on growth, IGF-I, and GH receptor (GHR) to those in control-fed and fasted fish. They demonstrated a reduction in growth in cortisol-fed fish compared with control-fed fish and weight loss in the fasted fish. Plasma IGF-I concentrations were significantly reduced in both the cortisol-fed and fasted fish, as was hepatic mRNA expression of GHR. Their results indicated a positive correlation between GHR expression and circulating IGF-I levels in both cortisol-fed and fasted channel catfish. Small et al. (2006) thus concluded that reduced GHR expression in the liver might serve as a mechanism for the reduction of circulating IGF-I and corresponding growth retardation in channel catfish during periods of food deprivation and stress.

The observed increases in hepatic transaminase (enzyme number 2.6.1.5; IUBMB 1992) activity, downregulation of GHR, and induction of a 20-kDa IGFBP coupled with decreased body fat and liver size indicate that cortisol reduces growth by suppressing IGF-I activity and activating gluconeogenic and lipolytic mechanisms for energy production during stress (Table 3). Of further interest are the apparent similarities in growth and somatotropic axis modulation between cortisol-fed and fasted channel catfish. The observed increase in plasma cortisol in fasted fish (Peterson and Small 2004) and corresponding changes in IGFBPs further demonstrate the role cortisol plays in energy partitioning.

Reproduction

Knowledge of how a stressor might affect reproductive physiology is important to managing a captively breeding fish population and can be monitored in terms of the number and quality of progeny. The effects of stress on fish reproduction, gamete quality, and progeny have been reviewed by Schreck et al. (2001). It is clear that species of fish differ in their physiological response to stress and in the resulting reproductive consequences. Schreck et al. (2001) discussed how fish under stress may assume a different mode of operation to maintain homeostasis, known as allostasis, that is adaptive for keeping the parent alive but may be maladaptive for reproductive fitness. Much of the data available concerning the effects of stress or cortisol on reproductive success in fish is inconsistent. Some of this is undoubtedly a result of variation among species and the type and magnitude of the stressor.

Schreck et al. (2001) suggested that to understand the effects of stress on reproductive fitness, one must consider the gonadal development stage at which the stress occurs because different energy allocation responses may occur. As proposed by Roff (1982), there are two general responses to stress in fish undergoing gonadal maturation: (1) maintenance of body weight and adjustment in gamete production and (2) maintenance of egg number at the cost of somatic tissue. For example, stress to broodfish during vitellogenesis may result in atresia and egg reabsorption, while loss of somatic tissue may result from insufficient nutrition or other factors that prevent maintenance of both growth and egg number. Ultimately, the decision that must be made when broodfish are exposed to stressful situations is whether or not to reproduce. Once again, this appears to be determined in part by the timing of the stressor relative to the stage of gonadal maturation. Rainbow trout exposed to stress during late vitellogenesis ovulated earlier than nonstressed counterparts (Contreras-Sanchez et al. 1998). Rainbow trout exposed to stress for 9 months prior to spawning, however, had smaller eggs and delayed ovulation (Campbell et al. 1992).

The association between fish stress, elevations in plasma cortisol, and concomitant depressions in steroidogenesis (Pickering et al. 1987; Carragher and Pankhurst 1991), together with evidence that exogenous cortisol produces inhibitory effects on reproduction in fish (Carragher et al. 1989; Pottinger et al. 1991; Foo and Lam 1993; Clearwater and Pankhurst 1997; Cleary et al. 2000; Pankhurst 2001), has led to the general assumption that the effect of stress on fish reproduction is mediated through the action of cortisol on the gonad. However, in vitro studies of goldfish, common carp *Cyprinus carpio*, and snapper *Pagrus auratus* suggest that there is no inhibitory effect on steroidogenesis after treatment of follicles with cortisol, and in several cases augmented gonadotropin-induced estradiol production was demonstrated (Pankhurst et al. 1995). Studies of stinging catfish *Heteropneustes fossilis* establish perhaps the only clear physiological role for cortisol in teleost reproduction, providing evidence that gonadotropic action on oocyte maturation is mediated through cortisol's heterocorticotrophic action on oocytes to induce maturation (Sundararaj and Goswami 1977; Lamba et al. 1983).

Channel catfish have reportedly low annual spawning success in aquaculture ponds. Silverstein and Small (2004) reported typical spawning rates ranging from 8% to 80% and suggested that average rates are as low as 30% for the industry. As in other captive silurids

(e.g., African catfish *Clarias gariepinus*: de Leeuw et al. 1985; walking catfish *C. batrachus*: Manickam and Joy 1989; stinging catfish: Tharakan and Joy 1996), final oocyte maturation in channel catfish is often inhibited (Silverstein et al. 1999). Prior to the spawning season, channel catfish are typically sorted and moved to spawning ponds, creating stress in the broodfish. Historically poor overall spawning incidence, an abundance of literature suggesting that cortisol inhibits reproduction in many fish species, and inherent stressors associated with commercial broodfish management led Small (2004a) to assess the effects of exogenous cortisol on channel catfish reproductive success; the hypothesis was that cortisol would negatively affect reproductive output (number of spawning events) and fitness (fecundity and hatching rates).

Small (2004a) administered cortisol at 150 mg/kg in feed (ration = 1% body weight) to broodfish three times weekly for 11 weeks during late vitellogenesis leading up to spawning. Relative to the plasma cortisol level in control fish (7 ng/mL), cortisol was elevated fourfold (29 ng/mL) in cortisol-fed fish 6 h after the last feeding; this was associated with a substantial decrease in somatic growth and hepatosomatic index in cortisol-fed fish. Plasma glucose concentrations were also found to be higher in the cortisol-fed broodfish than in control fish. Cortisol did not appear to affect the timing of ovulation or frequency of spawning during the 10-week spawning period; however, cortisol-fed channel catfish had a nearly twofold increase in spawning incidence and no observable changes in egg size, fecundity, or hatching success relative to controls. Small (2004a) concluded that (1) the observed results were contradictory to what was hypothesized and (2) although the majority of available literature indicates a negative effect of stressors on reproductive fitness in fish through modified endocrine function (Pankhurst and Van der Kraak 1997), the interactions between cortisol and reproductive function may not be consistent among species. It is important to reiterate that the timing of stressors or cortisol administration relative to gonadal maturation is important in determining the response (reviewed by Schreck et al. 2001). In channel catfish given cortisol during late vitellogenesis, spawning incidence was increased at the expense of somatic growth (Small 2004a). This may have been an adaptive response to ensure genetic succession at a cost to the parent or perhaps reflected the role of cortisol as a maturation-inducing steroid in channel catfish, similar to observations in walking catfish. Although further investigation is necessary to assess the mechanisms involved, one thing is clear from Small's (2004a) study: no causal effects of cortisol on reproductive dysfunction are evident for channel catfish.

Selective Breeding

Selective breeding has been used to develop strains of rainbow trout with high and low tolerance to stress as indicated by poststress increases in cortisol (Fevolden and Røed 1993; Pottinger et al. 1994; Pottinger and Carrick 1999). Growth rate, feed intake, and feed efficiency all appear to be improved in rainbow trout selected for a low stress response (Trenzado et al. 2006). Greater feed efficiency has also been observed in African catfish that exhibit a low cortisol response to a 1-h stressor (Martins et al. 2006). Furthermore, higher stress tolerance in rainbow trout appears to be correlated with less wasted feed (Øverli et al. 2006). This is presumably because appetite is relatively less affected by external stressors in fish with low stress responses. Recent results with channel catfish also suggest low stress responsiveness correlates with improved growth. Peterson et al. (2008) demonstrated a negative correlation ($r = -0.47$; $P < 0.05$) between channel catfish weight gain and plasma cortisol response after application of a 10-min confinement stressor to fast- and slow-growing families. In a separate study, plasma cortisol concentrations of three channel catfish strains known to have different growth rates were not reportedly different after 1 h of confinement stress and 1 h of recovery (Bosworth et al. 2004). Taken together, these results suggest that the rate of cortisol increase is more indicative of channel catfish growth potential than is the maximal cortisol response.

As the field of stress physiology advances, new opportunities for improving fish performance by utilizing components of the HPI stress axis as potential genetic markers or candidate genes are likely to present themselves. In addition to those studies already reviewed that demonstrate the effects of cortisol on growth-related genes such as IGF-I (Peterson and Small 2005) and GHR (Small et al. 2006), others have begun to look more closely at genes involved in the stress response in channel catfish (Karsi et al. 2005) and at the interactions of stress response components with genes involved in muscle development (Weber and Bosworth 2005; Weber et al. 2005). As we learn more about the regulation of stress-related genes and their interaction with genes involved in fish performance, marker-assisted selection comes closer to a reality for use in selective breeding.

Summary

A great deal of research has been conducted over the years to better understand the stress response in fish.

While cortisol has traditionally been the focal point for much of this research, the relationship between observed cortisol increases in response to stress and the physiological consequences affecting phenotypic expression have received much debate. Some of the attributed discrepancies in the literature can undoubtedly be associated with the diversity of techniques used to elicit a stress response and the variety of fish species examined. It is often tempting to draw general associations and conclusions about "fish," but consideration must be afforded to differences in species evolution and life history strategies (reviewed by Barton 2002).

Channel catfish are the leading aquacultural product in the United States, and yet our understanding of their physiology is very limited. Progress has been made toward selecting domesticated channel catfish with improved production characteristics (Dunham and Smitherman 1983; Wolters et al. 2000), but variable disease resistance, growth, and reproductive success in captivity are hurdles that must be overcome for the U.S. industry to be competitive with foreign imports. Stress is a common factor affecting these economically important traits. This review emphasizes just how little is known in that regard but also presents the progress that is being made toward defining the physiological consequences of both stress and cortisol on disease susceptibility, growth, and reproduction. It is clear from the studies reported here that circulating cortisol concentration is not always the best indicator of the physiological consequences of stress in channel catfish. Although chronic stress can be detrimental to fish, the immediate stress response is probably one of adaptation in an effort to reallocate energy to where it is needed most.

This brief review has reported the effects of stress and cortisol on channel catfish disease susceptibility, growth, metabolism, and reproduction. Of these, growth appears to be the most easily understood. Like most fish, channel catfish respond to stress with decreased feed intake and reduced growth. Cortisol appears to be a causative factor in growth reduction and the associated energy reallocation, as demonstrated by its direct effects on the somatotropic axis and lipid and protein metabolism. The distinction between the overall stress response and the effects of cortisol on disease susceptibility in channel catfish is less clear. Overall, there is evidence suggesting that stress lowers the ability of channel catfish to resist some pathogens, but cortisol does not appear to inherently be the causative immunosuppressive agent. Even less certain are the effects of stress and cortisol on channel catfish reproduction. Based on the study by Small (2004a), cortisol appears to stimulate ovulation when administered late in vitellogenesis. It remains unclear whether cortisol acts as a maturation-inducing steroid or simply causes a survival-type response to preserve the developing oocytes and reproduce.

As research continues to define the role of cortisol in modulating physiological responses during stress and begins to tease out causative factors that work separately from or in conjunction with cortisol, initial improvements in managing the stress response of cultured fish can be made, whether through genetic selection, pharmaceuticals, or physical or environmental changes. It is apparent, however, that species-specific knowledge of relationships with targeted production traits is necessary before effective strategies for mitigating the stress response in channel catfish can be appropriately and fully developed.

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