RELAÇÃO ENTRE IGF-I E CORTISOL NO CRESCIMENTO DE PEIXES TELEÓSTEOS DE PRODUÇÃO - REVISÃO SISTEMÁTICA

RELATIONSHIP BETWEEN IGF-I AND CORTISOL IN THE GROWTH OF PRODUCTION TELEOST FISH – A SYSTEMATIC REVIEW

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RESUMO

A exposição ao estresse pode ocasionar redução na produtividade na piscicultura. Um somatório de mudanças fisiológicas é desencadeado em resposta ao estresse, sendo o cortisol um dos principais hormônios relacionados com o sistema do hormônio do crescimento/fator de crescimento semelhante à insulina/proteína de ligação do fator de crescimento semelhante à insulina (GH/IGF-I/IGFBP). O objetivo deste estudo foi verificar a relação entre IGF-I e cortisol em peixes teleósteos e com isso avaliar o efeito do estímulo de estresse na produção destes animais. A pesquisa eletrônica foi realizada através da pesquisa na base de dados Web of Science no mês de março de 2010. Foram analisados fatores relacionados à espécie de peixe, tipo de estudo (*in vivo* ou *in vitro*), tamanho da amostra, método de quantificação hormonal, relação entre IGF-I e cortisol e tipo de indução ao estresse. A avaliação quantitativa e qualitativa da literatura atribuiu ao cortisol a função de hormônio inibidor do crescimento. As diferentes metodologias de mensuração hormonal juntamente com a diferença de especificidade entre os kits utilizados nos diversos trabalhos, além da diversidade de concentrações hormonais e de técnicas de aplicação, somado a diversidade de espécies abordadas podem ocasionar divergências dos resultados relatados.

Palavras-chave: Cortisol, Crescimento, Estresse, IGF-I, Piscicultura.

ABSTRACT

Exposure to stress can lead to reduced productivity in aquaculture. Several physiological changes are triggered in response to stress, and cortisol is a major hormone that can also interfere with the growth hormone/insulin-like growth factor/insulin-like growth factor binding protein (GH/IGF-I/IGFBP). The aim of this systematic review was to assess the relationship between IGF-I and cortisol in teleost fish and thus evaluate the effect of stress stimulus in the production of these animals. The electronic survey was conducted by searching the database Web of Science in March 2010. We analyzed factors related to fish species, type of study (*in vivo* or *in vitro*), sample size, method of hormonal quantification for cortisol and IGF-I and typeinducing stress. The quantitative and qualitative assessment of the literature attributed to cortisol a growth inhibition function. Different methods of measuring hormones, along with the differences in the kits used in many studies, and in hormonal concentrations, application of techniques and the diversity of species, created a wide range of reported results.

Keywords: Aquaculture, Cortisol, Growth, IGF-I, Stress.

INTRODUCTION

The teleost fish, both in nature and in artificial conditions, are often exposed to stressful situations. Under conditions of aquaculture, the natural challenges are composed by those imposed by the activity itself, as management practices, transportation, high stocking densities, temperature, photoperiod and water quality (LIMA et al., 2006). This situation creates a problem for fish production, and consequently the financial return to this activity.

The sum of the physiological changes triggered when the fish react to chemical challenges, physical and biological attempt to compensate are more commonly referred to stress responses and lead to endocrine alterations (LIMA et al., 2006). The plasma cortisol, known as the stress hormone, has an interest in reproductive performance and its mechanism of action appears to involve the system of growth hormone insulin-like growth factor/insulin-like growth factor binding protein (GH/IGF-I/IGFBP) (MOMMSEN et al., 1999).

IGF-I is the hormone involved in cell growth and it is produced mainly in the liver under the regulation of GH (DEANE; WOO, 2005). It acts through activation of receptors located in the target organs, coupled to IGFBPs. According to the literature, there is a relationship between IGF-I and cortisol, but there is no consensus regarding the relationship between these two hormones, especially in several species of fish. Jiao et al. (2006) found that injection of cortisol in bream (*Sparus aurata*) increased the expression of liver GH receptor (GHR-I), thereby increasing the production of IGF-I.

On the other hand, in tilapia (*Oreochromis niloticus*), the intraperitoneal injection of cortisol resulted in reduced expression of IGF-I in the liver and its plasma concentration (KAJIMURA et al., 2003). Davis et al. (1985), Small (2005) and Peterson and Small (2005) also observed that administration of cortisol in the diet reduced the plasma concentration of IGF-I in tilapia and catfish, and consequently decreased the rate of growth in these fish.

Faced with the need to reduce the effect of the stress cortisol in fish and trying to maximize production rates and profitability, it is necessary to know the relationship between IGF-I and cortisol and the influence of these hormones in the growth rate of fish.

Therefore, the objective of this study was to systematically review the relationship between IGF-I and cortisol in teleost fish.

CONTENTS

MATERIALS AND METHODS

Search strategy and selection of scientific articles

The selection of articles was performed by searching the database Web of Science (http://www.isiknowledge.com) using the following keywords: cortisol AND IGF-I and fish. The review of the literature covered studies published up to March 2010.

Initially, 51 papers were retrieved, of which 14 were excluded as they were literature reviews and nonrandomized scientific articles, thus resulting in 37 articles. Subsequently, another refinement was carried out in order to select only those articles where the issue addressed specifically the relationship between IGF-I and cortisol on the growth of teleost fish, summarizing this way 12 articles in total. The entire selection process was carried out by two researchers separately and refinement of the selected articles was conducted at a consensus meeting. A 100% agreement was obtained at this stage between the two researchers.

The 12 papers that met the criteria have been thoroughly reviewed by the authors of this paper. Analysis of the experimental design, sample size, method of detecting hormone, the species used, the dosage of hormone used, the relationship between IGF-I/cortisol and quality of methodology were performed, compared and presented in Table 1. When differences were found among the studies, these were discussed among the authors in order to develop a qualitative scoring scale.

Qualitative analysis of the literature

Not all parameters used were scored on the quality scale, but were taken into consideration for being relevant to the subsequent discussion. Adapted based on other systematic reviews (NEGRI et al.; 2009; PEREIRA et al., 2011), some parameters were classified as adequate (score: 1) or not sufficient/inadequate (score: 0).

The articles were ranked according to the following criteria:

1) Articles that used a sample size less than 10 received the score 0 and those who used greater than or equal to 10 received a score of 1.

2) Articles that have involved only *in vitro* analysis received a score 0 and those who tested *in vivo* models, received a score of 1.

3) Articles that used immunofluorescence, ELISA, radioimmunoassay (RIA) and real-time PCR, very precise and sensitive methods to quantify hormones, received a score of 1 and articles that used other methodologies received the score 0.

The final score for each scientific paper was found by the sum of points obtained in each of the three criteria mentioned above, the minimum score being zero and three the highest score.

RESULTS AND DISCUSSION

By combining the methods of search, 12 papers met all inclusion criteria. Table 1 describes the 12 scientific studies related to: score of the paper, the species used, *in vivo* or *in vitro* methods, sample size, method of quantifying hormone and the type of stress induced to the animals. Seven articles have achieved maximum score (three points), whereas three articles were classified as intermediate (two points) and only two reached only one point according to the criteria adopted. In general, different approaches have been made by researchers as an attempt to understand the relationship between cortisol and growth factors. In these studies, the effects of different stressors in different species of fish were tested.

It was found that with 15 minutes of exposure to stress by confinement, there was a decrease in IGF-I after two hours and no changes occurred in the levels of IGFBPs depending on the elevation of plasma cortisol in *Sunshine bass* (DAVIS; PETERSON, 2006). However, this same research, the daily supply of a single meal containing 100 mg cortisol/kg increased the concentration of cortisol in plasma, but did not influence the levels of IGF-I and of IGFBPs. On the other hand, Peterson and Small (2005) found that in "channel catfish", the weight gain, food intake and IGF-I concentration was lower when higher doses of cortisol were used in the diet (200 and 400 mg/kg). One mechanism by which cortisol can prevent the growth of "channel catfish" is through an increase of ~ 20 KDa IGFBP which may lead to inhibitory effects on the action of IGF-I, since the IGFBPs play central role in coordinating and transporting IGF-I in the blood and through the capillary barrier to target tissues, prolonging the half-life of the hormone (BAXTER, 1994; FERRY et al., 1999; ROSENFELD et al., 1999; ROSENZWEIG, 2004). In addition, Peterson and Small (2005) found that cortisol can suppress the gene expression of IGF-I. This theory was based on the fact that the decrease in concentration of this hormone in the group of animals that received 200 mg cortisol/kg did not alter the concentration of mRNA for GH. Thus, it is suggested that the sensitivity of the production of IGF-I by GH is decreased by cortisol. This finding is also in accordance with Kajimura et al. (2003) in *Oreochromis mossambicus* and Leung et al. (2008) in *Sparus Sarba*.

Table 1. Search results for studying the relationship between IGF-I and cortisol on the growth of teleost fish.

	McCormick et al. (1998)	**Mancera and McCormick (1999)**	**Kajimura et al. (2003)**	**Aas-Hansen et al. (2005)**	**Peterson and Small (2005)**	**Small (2005)**
Article score	3	1	2	3	2	3
Fish species	*Salmo solar*	*Fundulus heteroclitus*	*Oreochromis mossambicus*	*Arctic charr*	*Ictalurus punctatus*	*Ictalurus punctatus*
Randomized	Yes	Yes	Yes	Yes	Yes	Yes
In Vivo*/*In Vitro	*In Vivo*	*In Vivo*	*In Vivo*	*In Vivo* e *In Vitro*	*In Vivo*	*In Vivo*
Number of animals per group	Exp. 1 – 20 Exp. 2 – 33/34	Not clear	Not clear	12	Exp. 1 – 7 Exp. 2 – 9	10

Methodology of hormone quantification	Cortisol: EIA IGF-I: RIA	Not performed	IGF-I: RIA; IGFPs: Western blot	RIA	IGF-I: competitive TR-FIA; Cortisol: DELFIA®	heterólogo TR-FIA
Cortisol effect	There was no relationship	Indirect action on the axis GH/IGF-I	Reduction of IGF-I mRNA levels in the liver. Increase in plasma IGFBPs	Reduction of IGF-I	Decreased concentration of IGF-I due to increased levels of IGFBPs	There was no relationship
Type of stress-inducing	Persecution, exclusion or draining the tank	Cortisol and IGF-I (injectable)	Different doses of cortisol (injectable)	Cortisol and IGF-I (injectable)	Cortisol in the feed	Fasting

Table 1. Continuation...

	Carnevali et al. (2006)	**Davis and Peterson (2006)**	**Liebert and Schreck (2006)**	**Kamangar et al. (2007)**	**Leung et al. (2008)**	**Saera-Vila et al. (2009)**
Article score	3	2	3	3	1	3

Fish species	*Dicentrarchus labrax*	*Sunshine bass*	*Oncorhynchus mykiss*	*Persian sturgeon (Acipenser persicus)*	*Sparus sarba*	*Sparus aurata*
Randomized	Yes	Yes	Yes	Yes	Yes	Yes
In Vivo*/*In Vitro	*In Vivo*	*In Vivo*	*In Vivo*	*In Vivo*	*In Vitro*	*In Vivo*
Number of animals per group	40000	6	35	12/13	4	10
Methodology of hormone quantification	Cortisol: EIA; IGF-I: PCR	RIA	RIA	IGF-I: RIA; Cortisol: RIA	IGF-I: quantitative rt-PCR	Cortisol: EIA; IGF-I: RIA; GHR-I, GHR-II, IGF-I and IGF-II: quantitative rt-PCR
Cortisol effect	Reduced the levels of IGF-I	Reduction of IGF-I	Reduction of IGF-I in fish stressed, one day after stress	There was no relationship	Cortisol inhibited the IGF-I expression	Reduction of GHR-II transcription and IGF-I in liver

Type of stress-inducing	No stress	Cortisol in the feed	Confinement	No stress	Different doses of cortisol (injectable)	No stress

RIA – Radioimmunoassays; EIA - enzyme immunoassay; TR-FIA - time-resolved fluoroimmunoassay; DELFIA® - time-resolved fluroimmunoassay kit

In the study by Liebert and Schreck (2006), investigating juvenile *Oncorhynchus mykiss* found that IGF-I did not show an immediate response to stress in freshwater, but after transferring to salt water, the authors found higher concentrations of IGF-I in the first and fourteenth days in control fish that were not subjected to stress in freshwater. Induction of stress did not impair feed intake of fish, but the results of this study suggested that food intake was reduced by changing the aquatic environment (freshwater to saltwater). In a more quantitative study with rainbow trout, Gregory and Wood (1999) demonstrated that implantation of cortisol in fish significantly reduced the individual food consumption. In addition, Bernier et al. (2004) found in "goldfish" that the efficiency of feed conversion was significantly reduced in the groups of fish fed with low and high concentration of cortisol diets.

Kamangar et al. (2007) did not observe any correlation between cortisol and IGF-I hormones in *Acipenser persicus* breeders during the growth and reproduction. This result contrasts with studies involving teleosts (KAJIMURA et al., 2003; PIERCE et al., 2005), suggesting different responses among different species of fish to stress.

Some studies have suggested that probiotic bacteria can minimize changes in plasma cortisol contributing to the control of pathogens and preventing them from diseases caused by stressors such as high density storage, handling and impaired water quality. The use of *L. delbrueckii* as a probiotic had a positive effect on the welfare and growth of juvenile sea bass (*Dicentrarchus labrax*, L.) (CARNEVALI et al., 2006). In this study, administration of probiotic decreased cortisol levels and affected the transcription of IGF-I and myostatin (MSTN), another factor related to body growth. Unlike IGF-I, myostatin is a protein produced in skeletal muscle cells that appears to delay the development of "stem cells" muscle, limiting the growth of muscle tissue. The increased transcription of IGF-I and MSTN inhibition of transcription resulted in increased body growth of animals that received the probiotic. These findings also suggested a relationship between IGF-I, cortisol and MSTN in control of body growth.

Acute stress confinement in juvenile *Sparus aurata* associated with increased levels of cortisol (3,0 ng/mL at 60-70 ng/mL) significantly reduced the transcription of growth hormone receptor II (GHR-II) in the liver. These proteins are important in the functioning and stimulation of the GH/IGF-I (SAERA-VILA et al., 2009). This suggests that changes in the strength of transcription of GHR-II can also be an indirect effect of cortisol on the synthesis of IGF-I. In contrast, Jiao et al. (2006) reported increased hepatic expression of a protein similar to GHR-I in *Sparidae* fish family.

McCormick et al. (1998) studied the relationship of cortisol levels and growth of juvenile Atlantic salmon (*Salmo salar*). Although the rate of growth significantly decreased in stressed animals, the plasma cortisol levels was significantly lower than controls, before and 3 hours after stress. Small (2005) also found that fasting had little influence on GH plasma levels, but it reduced plasma levels of IGF-I and cortisol. No relationship between cortisol and IGF-I was reported in this study. These results suggest that the suppression of growth in chronically stressed fish may be mediated by factors other than simply cortisol levels.

Overall, among the various stressors that may be present in intensive crops, water quality, fish handling, food and biological interactions are the most important from the standpoint of production. Studies that aim to minimize the stress of these fish are of extreme importance to minimize physiological and metabolic effects that impair the growth and survival of important species for aquaculture. Thus, the understanding of environmental change and the interaction of cortisol with IGF-I allows the identification of adverse conditions and develop methods to mitigate the negative effects of cortisol on fish health.

Importantly, the basal level of plasma cortisol may vary between different species of fish. For example, in salmonids under resting conditions, the value is around 10 ng/mL; in *Leuciscus cephalus* is approximately 250 ng/mL (POTTINGER et al., 2000) and *Brycon amazonicus* around 90 ng/mL (MARTINS DA ROCHA et al., 2004). However, in situations of acute stress such as handling, there may be a rapid increase in plasma cortisol, reaching values of 40-200 ng/mL in salmonids. These plasma cortisol levels may return to baseline within hours. When the fish is exposed to repeated and chronic stressors, the plasma cortisol level remains high for days and even weeks (OBA et al., 2009).

The different methods of hormone measurement with the difference in focus between the kits used in many studies, beyond the range of hormonal concentrations and application techniques, coupled with the diversity of species can be addressed reasons for the range of reported results. As mentioned in most studies, one of the methods used for analysis of IGF-I in fish is the technique of radioimmunoassay (RIA), which began in salmonid fishes. This method, which later extended to other species, was a crucial step toward defining the role of IGF-I in fish. However, other non-radioactive techniques as the "time-resolved fluroimmunoassay" (TR-FIA) have been described and validated to measure plasma concentrations of IGF-I in important species for aquaculture production. These two techniques together with direct enzyme immunoassay (EIA) have been used to quantify the levels of plasma cortisol. Other techniques such as PCR and Western Blot allow a more careful analysis of the effect of cortisol on the process of synthesis of IGF-I and the level of proteins (IGFBPs) that can interfere with their action on tissues, respectively.

CONCLUSION

This quantitative and qualitative assessment of the literature reported a growth inhibition function of the hormone cortisol, involving the axis GH/IGF-I/IGFBP in most of the studied species. It was observed cortisol tend to reduce the mRNA expression of IGF-I or GH receptor in the liver and increasing plasma levels of IGFBs, which can lead to a reduction in IGF-I action on tissues, eliminating thus the growth of fish. However, cortisol can not be the only factor regulating growth in some species. The type of stress is also a factor that should be taken into consideration, as cortisol levels may even reduce in some cases.

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