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Neuro-endocrine pathways in the control of stress in fish

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Abstract
The increasing intensification and subsequent contamination of many bodies of natural water bodies around the world by several anthropogenic substances is creating the major category of environmental stressor. Various stressors are necessary components of modern intensive fish culture (e.g., grading, transportation). The initial response represents the perception of an altered state and initiates a neuroendocrine/endocrine response that forms part of the generalized stress response in fish. This response includes the rapid release of stress hormones, such as catecholamines and cortisol into the circulation. Catecholamines are released from the chromaffin tissue situated in the head kidney of teleost's and also from the endings of adrenergic nerves. Cortisol is released from the interrenal tissue, located in the head (anterior) kidney, in response to several pituitary hormones, but most potently to adrenocorticotrophic hormone (ACTH). A recent study showed that ACTH may also stimulate adrenaline release and that chronic cortisol treatment may affect catecholamine storage and release in trout. As both the chromaffin tissue and the interrenal tissue lie in close proximity in fish, it is suggested that there is a possibility that a paracrine control for stress hormone regulation exists in fish. The response of the fish to such stressors involves all levels of organization, from the cell to the individual organism to the structure of the population. Stress response in fish is characterized by the activation of hypothalamo-pituitary- interrenal axis or HPA, activation of which starts in the pre-optic nucleus of hypothalamus (NPO) otherwise known as nucleus preopticus, which release corticotrophin releasing hormone (CPH). CPH, in turn, stimulates pituitary to release ACTH, which stimulates head kidney to release cortisol. Other pathways such as hypothalamo – pituitary – interenal (HPI) & pituitary – thyroid (PT) axis play an important role in stress control.

Keywords: HPA, HPI, PT, Chromaffin tissue, pre, optic nucleus, ACTH, CTH

Introduction

Now a day a growing demand for increasing yield per hectare of water body invited unlimited pressure on aquatic environment and the organisms sustain in it. With the implementation of intensive farming practices, the stress to all forms of aquatic life and the ecosystem in which these forms are a part, has increased manifold. Then what is stress? Stress is a state of mental or emotional strain or tension resulting from adverse or demanding circumstances. Stress in aquatic system is somewhat different from that of the terrestrial one and may be classified as physical, chemical, anthropogenic and genomic though there are several other forms. Depending upon the species composition and other natural phenomena each ecosystem is subjected variable and unpredictable stress, which is somewhat difficult to understand at its primary stage. Stressed ecosystem are characterised by a "distress syndrome" (Rapport *et al*. 1985) and are indicated by reduced biodiversity, altered productivity, increased disease prevalence, reduced efficiency in nutrient cycle, increased dominance of exotic and short-lived opportunistic species.

Generally, the potential performance capacity of an animal (fish here) is delineated by its genotype but the environment also, in its different forms, modify, aggravate and or minimise stress. Such as sub-optimal environmental temperature, though not stressful to fish, reduce growth rate in fishes. Actually environmental stress by way of producing constrains towards performance capacity creates a realized performance capacity when the normal performance is hindered and capacity of performance exists at that time after interacting with the specific stress or hindrance. In natural environment stress response is considered as an acute response which, otherwise force the fish to use energy, from its energy reserve, to overcome the situation evolved out of particular stress. In aquaculture perspective the environmental stress, if are of continuous or chronic in nature, expected to affect the health status of fish making it more susceptible to disease (Pickering and pottinger, 1989) [6]. The resultant interaction may lead to interfere with the reproductive performance as well reduce the growth rate (Pickering 1990) [4]. Some examples are overcrowding, water quality deterioration, confinement, sub-lethal pollution and social interaction. Out of the several stress factor, environmental one are so powerful that it can counteract with the all potential advantages generated out of genetic manipulation; It is realized now that a clear understanding of the influence of stress response on the performance capacity of fish is imperative to exploit the new technique of molecular genetics to its fullest extent. It is reported (Sumpter, 1992) [12] that when growth rate is interacted then endocrine pathway are found to be involved indirectly endocrine pathway are found to be involved interacting with the environmental stress.

Hypothalaic–Pituitary–Interrenal Axis (HPA) In Stress Response

Stress response in fish is characterized by the activation of hypothalamo-pituitary- interregnal axis or HPA, activation of which starts in the pre-optic nucleus of hypothalamus (NPO) otherwise known as nucleus preopticus, which release corticotrophin releasing hormone (CPH). CPH, in turn, stimulates pituitary to release Adreno-corticotrophic (ACTH) hormone, which is cleaved from proopiomelanocortin (POMC), ACTH stimulates head kidney to release cortisol. So the transmission of response to stress is an excellent example of neuro - endocrine control over stress. This elevation of cortisol level in plasma used as a quantitative measure of the magnitude of stress response. It is very likely that the adaptive significance this hormone is evident from its energy mobilizing properties (through gluconeogenesis), (Janssen and waterman, 1988) [3] Again, ionosmoregulatory properties help the fish to regain ionic balance during recovery from stress The elevation of cortisol level in plasma and its subsequent recovery to optimum base level is dependent on the type of stress acting on the fish. In case of handling; which produce acute stress in fish, the cortisol level remains in elevated level only for few hours before they restore to normal base level. However, when the stresses are of chronic in nature, the cortisol level remain in elevated form for days and even week long. Under condition of chronically stressed fish, such as overcrowding, plasma cortisol level return to base level in spite of the presence of continued stress. This happened due to the presence of a down regulation cortisol receptors in the target tissue accompanied by an increase in the metabolic clearance rate of hormone (Redding *et al*., 1984a) [9] Again when fish are subjected to continuous social domination by the other members of the same species or are stressed by low Ph., Plasma cortisol level remain in elevated form for weeks without any sign of return to base level.

Now regarding catabolic part, in particular reference to chronically stressed fish, cortisol elevation leads to suppression of growth. Stresses at chronic level make the fish susceptible to disease with significant suppression of growth rate and disruption in normal reproductive function. It is very likely that along with HPI axis other components of endocrine system are also evolved when fish are subjected to environmental stress.

Growth Hormone in the Control of Stress

Growth hormone (GH) is a protenaceous non-genomic hormone secreted from the anterior part of pituitary gland and is supposed to be a potent hormone that, beside normal growth, is involved in stress control of fish.

Mode of Action

As a non-genomic hormone it mediates its activity through second messenger system (Ca2+) within the cell and produce two distinct effects within the target cell such as –

Direct Effects

In this phase the hormone, after binding with the receptor of target cell (for example adipose tissue) it stimulates catabolic breakdown of triglycerides and suppress their ability to take up and accumulate circulating lipids.

Indirect Effects

This effects are mediated primarily by insulin-like growth factor (IGF –I), a hormone secreted from liver and other tissues in response to growth hormone. Majority of the growth promoting effects of GH are mediated due to IGF-I acting on target cells. Another peptide, Ghrelin, secreted from stomach and binds with the receptors on somatotrophs and potently stimulates secretion of growth hormone.

Stress and Growth

Stress results in variable changes in plasma levels of GH. Pickering *et al.* (1991) [7] reported acute depressed plasma GH level, whereas chronic stress elevates it. Following the observation that plasma GH level is elevated in starved fish, it is hypothesized that the apparently paradoxical effects of chronic stress could have arisen from starvation effects. Similar observation is also reported where fasted fish possess higher GH level than well fed fishes, but both showed reduced plasma GH level in response to acute stress (Far bridge and Leather land, 1992). These studies indicate that there exists definitely a correlation between GH and stress, and between GH and cortisol but their action required further study. Again, the information relating to theeffects of stress and for cortisol on GH stimulation of IGF-I production or the tissue action of IGF-I needs further study

Transgenic GH Gene in Dealing Stressed Fish

Transgenic growth hormone gene (native or recombinant) remarkably stimulate somatic growth which is medicated through insulin –like growth factor (IGF-I) (Gitt *et al*., 1985) [2]. This exogenous GH- enhanced growth, achieved through increasing appetite and food conversion efficiency. It creates a new era in involving transgenic GH gene as a potent growth enhancer for stressed fish as well as the use of GH gene for direct gene manipulation, when the literature relating to endogenous GH and its role in fish physiology is scanty. On the contrary some other study indicated highly significant elevation in plasma GH level in moderately exercised fish which the same is depressed in exhausted fish. These were observed also when the fish are maintained in complete confinement for 24 hrs. It appears that more specific study is needed to understand the correlation between GH receptor and IGF activity in such a situation but it indicates the presence of some other physiological and endocrine mechanism relating to plasma GH suppression.

Two different studies have shown the stimulation of GH release by cortisol and increase in the response of internal to ACTH following GH treatment both in vitro and in vivo. Then the elevations of plasma GH in blood plasma of starved fishes indicate this effect to be independent of HPI actively. This indicate that the entire subject relating to growth hormone physiology along with its anabolic and osmo-regulatory role needs intense review through specific research programme before predicting specific comments.

Hypothalamic Pituitary Gonad Axis in Stress Control

Hypothalamic –pituitary –gonadal axis (PHG) plays a crucial role in the development and regulation of reproductive and immune system. In oviparous animal it is known as Hypothalamus–pituitary–gonadal–liver axis (fish, bird, reptiles etc.) in females. During sexual maturation of fish somatic growth is reduced and resources from the body muscles are directed for gonadal development under the influence of low level of anabolic steroid. This is evident from the fact that administration of methyl testosterone, a synthetic androgen, significantly enhances growth of some fishes. Some authors (Sergent, 1972). Similarly, established the growth promoting features of diethyl stilbestrol. These observations indicate that reproductive maturation in fish is dose dependent, because further elevation of these steroids directs the fish towards attaining final maturation with consequent reduction in somatic growth. 11- ketotestosterone, a nature steroid is effective in enhancing growth at early stage, when fed with diet (a) the rate of 2mg/kg body wt. Further increment of dose @ of 8 mg/kg, the hormone became ineffective, while @ of 32mg/kg growth is inhibited. These findings elucidate that gonadal steroids are anabolic at lower dose during the period of early maturation. Chronic stress(confinement) are found to suppress the levels of testosterone and 11- ketotestosterone in male, while cortisol treatment also supports the steroidal level in unstressed exhibiting similar mode of action. It is evident as we know that cortisol by acting on pituitary, suppress GTH secretion as result the secretion of gonadal steroids are inhibited in male. In female fish cortisol reduce gonadal steroid by inactivating hepatic oestradial receptors. Thus cortisol mediated growth suppression, during early stage of reproductive cycle, establish another pathway for stress induced growth suppression. Generally, GH stimulate steroidogenesis in fishes but stress-induced GH suppression found to decrease gonadal steroid level in plasma. The pituitary-gonadal axis and growth hormone activity are under the control of GNRH from hypothalamus.

Pituitary- Thyroid Axis

As in other vertebrate's thyroid gland of fish secretes thyroxine (T4) by being stimulated by TSH (Thyroid stimulating hormone) from pituitary. Mono-iodotirosinase convert T4 into T3 (Tri-iodothyronine), which is more potent than T4 due to its greater capacity to bind with the hormone receptor at target tissue cells. Both are anabolic at early developmental stage but T3 is more potent and both exhibit extra potency when applied with GH while chronic environmental stress suppresses thyroidal activity, specific stress of transfer reduces the plasma level of T4 and T3up to four times. Increased stocking reduces only T4. From this observation it is difficult to predict whether this suppression is director or under the control other phenomenon like reduced food intake. As the pituitary-thyroid axis is very much sensitive to nutritional status so this suppression may be related to reduce food intake. This axis is also sensitive to HPI axis and cortisol treatment and the levels of both the hormones are suppressed following cortisol administration though in specific stressed condition the level of the two hormones varies. Stress induced HPI axis reduces T3 levels in blood leading to growth suppression. GH stimulates conversion of T4 to T3 so GH suppression may lead to the reduction of thyroidal activity in stressed fish. As the responses of these hormones are dose dependent so specific study is required before concluding precise link between thyroidal and gonadal activity on PT axis

Other Endocrine Pathways

Catecholamine's, which otherwise known as stress or emergent hormones includes adrenalin(epinephrine) and nor-adrenalin (nor-epinephrine), secreted from chomaffin tissue acts as an invariable components of stress response in fish like other vertebrates. These hormones help the fish to overcome the immediate threat out of stress by bringing congenial changes in the vascular and respiratory system and also by mobilizing carbohydrate reserves. In stressed condition catecholamine's stimulate breakdown of glycogen in liver and muscle. The assumption that, both the catecholamine's, though catabolic pathways suppress growth of stressed fish but there is no evidence of their elevation in stressed fish.

HPI axis

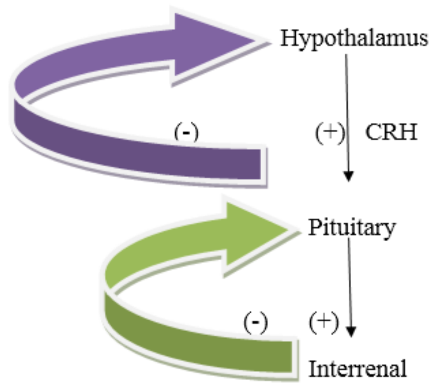

Fig 1: Hypothalamus- Pituitary-interrenal axis (HPI). Arrows are directed from the point of secretion of target organ. Positive (+) and negative (-) signs indicate feedback control mechanism. For example, cortisol produced in interregnal gland suppress corticotrophin releasing hormone from hypothalamus and Adreno - corticotrophin (ACTH) from pituitary gland.

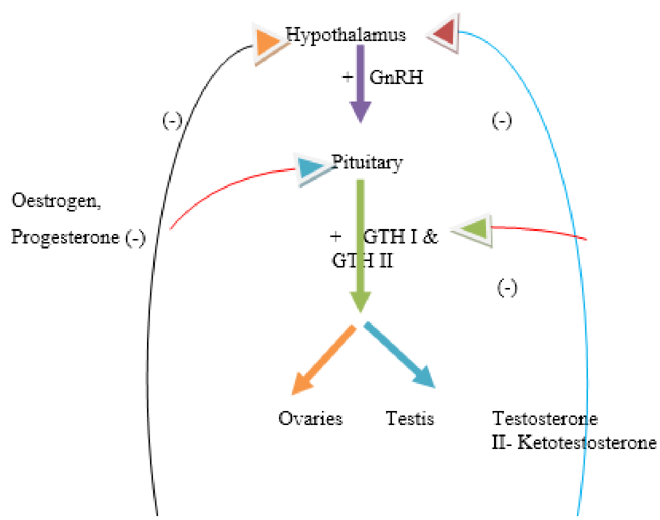

Fig 2: Hypothalamico- Pituitary-Gonadal axis

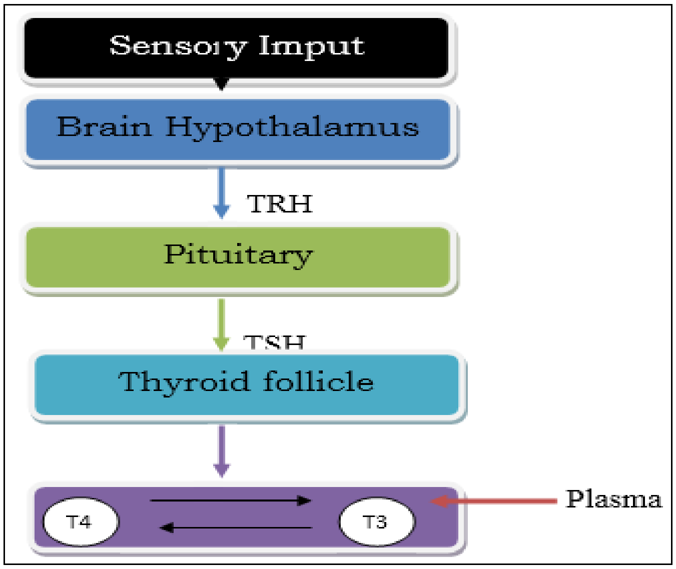

Fig 3: Hypothalamic- Pituitary- Thyroid axis

Stress–induced pathways and its implication in aquaculture

As indicated a variety of pathways are involved in stress-induced growth suppression in fish. So any problem to improve the potential growth by selective breeding or by direct gene manipulation, should consider the environmental impact. This is need, specially, when a program is implemented to maximize the return. Guidelines for minimising stress in aquaculture are already available (Colombo *et al*., 1990; Pickering *et al*. 1992) [1, 8]. It is now clear, through several experimental studies, that stress-induced HPI axis acts as the main component in grow suppression. So efforts should be directed to reduce the response to such stress through selective breeding or gene manipulation.

If this is achieved, it will create beneficial effect on disease resistance and reproductive performance. The work of Retstie (1982, 86) [10] indicated, like other vertebrates, that magnitude of cortisol response to stress is a heritable character. A comparison of cortisol response between two strains (wild & domesticated) of fish indicate that an empirical selection along this line has already been established, yet there still exists potential selection line and a seven-fold difference in the magnitude of cortisol response among different strains of same species has already been established by Pottigner *et al*. (1992). It is possible, through careful and repeated experiment, to identify fish with a consistently higher or low cortisone response to a standard form of stress such as short-term confinement. As it has already been confirmed that the magnitude of cortisol response to stress is a heritable character so further work is needed to accelerate selection process and to investigate the performance capacity, including growth rate, of the offspring under ideal environmental conditions and under conditions of chronic stress- as has been already established in the poultry industry.

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