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Effect of environmental stressors on fish health – Possible action of controlled stress as a eustress in fish

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Abstract: Fish are exposed to various local and global environmental stressors (or stimuli), such as pollutants, chemicals, acute and chronic changes in temperature, and the subsequent increased chances of succumbing to infectious diseases are concerned. The exposure of organisms to stressors may result in a series of biochemical and physiological changes. At the living state, these changes are mediated by the neuroendocrine system. There is also a cellular stress response, which includes the induction of stress proteins, a family of heat shock proteins, following exposure to stressful situations. These stress responses in organisms can affect their general health. We observed the decrease in the redox state in response to heat shock or high doses of dietary antibiotics, oxytetracycline (OTC), in coho salmon (*Oncorhynchus kisutch*). The results indicate that both heat shock and the high doses of dietary OTC induce oxidative stress, which would enhance oxidation in fish. In addition to physical and chemical stress trials, we found that mild physiological stress by handling can affect the expression of growth-related genes in fish. In general, the word "stress" has a negative connotation and is likely to be considered undesirable. However, the effects of stress differ depending on the intensity of the stimulus, the condition of the recipient, etc. It is considered that there are two types of stress: eustress (positive or desirable stress) and distress (negative or undesirable stress). Accordingly, eustress provided by environmental stresses under control in aquaculture, are useful to accomplish the maintenance and improvement of farmed fish health as well as fish welfare.

Keywords : *environmental stressor, oxidative stress, eustress, distress, fish*

1. Introduction

The production of farmed fish has increased in inverse proportion to a global decline in ocean fishery stocks. About half of the world's fishery production is based on aquaculture which has the potential to reduce fishing pressure on

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threatened stocks (Naylor *et al.*, 2000, Pauly *et al.*, 2002, Garlock *et al.*, 2019). Global food demand has been increasing. Food from the sea is originated from capture fisheries and aquaculture, and represents 17% of the current global production of edible meat (Costello *et al.*, 2020, FAO, 2020). In addition to protein, seafood is rich in functional polyunsaturated fatty acids and micronutrients, such as minerals, vitamins and carotenoids. Aquaculture is, therefore, important to be developed to support the increase of global food production. Global aquaculture production was estimated in 82 million tons of aquatic animals in 2018. At the time, aquatic animal farming was dominated by finfish (FAO, 2020). Aquaculture is supposed to become a major source of aquatic dietary proteins by 2050. Accordingly, it is important to develop methods to enhance the aquaculture production and to evaluate the impact of aquaculture on the environment.

Fish are exposed to various local and global environmental stressors (or stimuli), such as pollutants, chemicals, acute and chronic changes in temperature, and the chances of succumbing to infectious diseases may be increased subsequently (Iwama *et al.*, 2006, Nakano, 2016, Afonso, 2020, Nakano, 2020, Nakano and Wiegertjes, 2020, Nakano, 2021a, 2021b, 2022, Schreck and Tort, 2016, Sneddon *et al.*, 2016, Sopinka *et al.*, 2016). The stress induced by environmental stressors in fish is thought to influence their fitness, productivity, health, and quality after catch. Therefore, the control of stress is considered to be very important in farmed fish. However, overall knowledge of stress response and protection against stress in fish is less comprehensive than that in mammals.

The objective of this article is to summarize knowledge concerning stress response to environmental stressors in fish. The possibility that controlled environmental stress might act as a eustress (positive or desirable stress) in fish is also discussed. (Niki, 2007, Okegbe *et al.*, 2012, Kupriyanov and Zhdanov, 2014, Afonso, 2020, Nakano, 2021a, Yamauchi and Suto, 2022).

2. Stress response in fish

Stress is likened to a dented rubber ball pushed with fingertips. The pressure (stimulus) of the external factor which causes the stress (dented state) is originally regarded as a stressor (Bannai, 1994, Nakano, 2021a). Stressors can be classified into three categories: (1) physical and chemical stress in response to detrimental temperature, ultraviolet rays, and radiation; (2) physiological stress caused by exercise, handling, and infection; and (3) psychological stress caused by intimidation and anxiety. The stress response can be divided into three phases, warning response, resistance, and exhaustion (Iwama *et al.*, 2006, Nakano, 2016, 2020, 2021a, Schreck and Tort, 2016, Sneddon *et al.*, 2016, Sopinka *et al.*, 2016).

The homeostasis of the organism is achieved through the formation of a network with the central nervous system as the control tower, the endocrine system for hormone secretion, and the immune system for biodefense (Barton and Iwama, 1991, Schreck, 1996, Schreck and Tort, 2016, Sneddon *et al.*, 2016). In general, the exposure of fish to stresses may result in a series of biochemical and physiological changes. Although maintaining homeostasis should be a key process to cope with stress, these changes would be an important aspect of the adaptive response (Iwama *et al.*, 2006, Nakano, 2016, Afonso, 2020, Nakano, 2020, Nakano and Wiegertjes, 2020, Nakano, 2021a, 2021b, Schreck and Tort, 2016, Sneddon *et al.*, 2016).

The stress response to exogenous or endogenous stressors in fish has been divided into first,

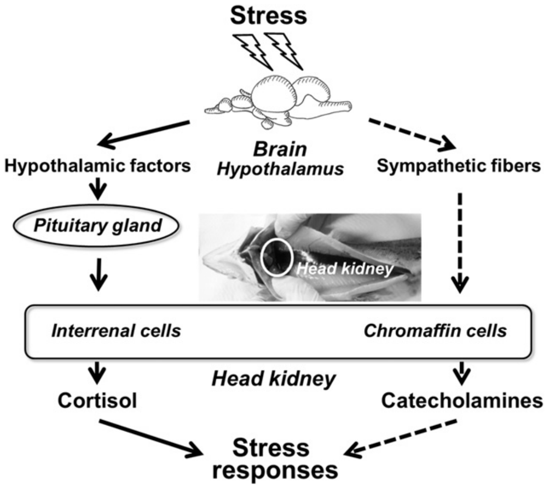

Fig. 1 Schematic view of the primary stress response, a neuroendocrine response, in fish. The solid and broken lines indicate hypothalamic-pituitary-interrenal cell (HPI) axis and hypothalamic-sympathetic-chromaffin cell (HSC) axis, respectively.

second, and third phases. The primary response represents the perception of an altered state and initiates a neuroendocrine reaction, resulting in the rapid release of stress-related hormones, such as catecholamines (dopamine, norepinephrine, adrenaline, etc.) and cortisol, into the blood circulation system through the two neuroendocrine pathways. Catecholamines and cortisol activate many metabolic pathways. The two systems shown in Fig. 1 are the hypothalamic-pituitary-interrenal (adrenal cortex in mammals) system (cortisol or HPA systems) and the sympathetic-chromaffin (adrenal medulla in mammals) system (adrenaline or SAM systems). The interrenal and chromaffin cells are present within the head kidney in fish. Hence, in fishes, the stress hormone cortisol is secreted from the head kidney (anterior portion of the kidney), which corresponds to the mammalian adrenal cortex and medulla. The magnitude of the stress hormone response depends on several factors including the type and degree of stresses, and fish species (Barton and Iwama, 1991, Schreck, 1996, Basu *et al.*, 2001, Iwama *et al.*, 2006, Nakano, 2020, 2021a, 2021b, Gorissen and Flik, 2016, Schreck and Tort, 2016, Sneddon *et al.*, 2016, Sopinka *et al.*, 2016, Winberg *et al.*, 2016). The secondary stress response is composed of various biochemical and physiological adjustments associated with stress and these are mediated by several stress hormones. For example, the production of glucose from glycogen in response to stress provides fish with energy substrates to tissues in order to cope with the increased energy demand (Barton and Iwama, 1991, Iwama *et al.*, 2006, Nakano, 2020, 2021a, 2021b, Schreck and Tort, 2016, Sneddon *et al.*, 2016, Sopinka *et al.*, 2016). The tertiary stress response represents the reaction of the whole-organism associated with stress, including reduced growth, decreased reproduction, impaired immune system , and reduced survival (Iwama *et al.*, 2006, Nakano, 2016, 2020, 2021a, 2021b, Schreck and Tort, 2016, Sneddon *et al.*, 2016, Sopinka *et al.*, 2016).

In addition to the neuroendocrine stress response following exposure to stressful situations, there is a cellular stress response. At the cellular level, some stresses, such as the increased levels of temperature and hypoxia, and changes in salinity, may lead to the induction of a family of heat shock proteins (HSPs), which are highly conserved cellular proteins in all organisms, including animals and plants. Extensive studies on model species have revealed three major families of HSPs: HSP70, HSP90, and low molecular weight of HSPs. There is a constitutive production of these proteins known as a heat shock cognate, which is essential in various aspects of protein metabolism in unstressed cells in addition to the HSPs (Richter *et al.*, Iwama *et al.*, 1998, Basu *et al.*, 2001, Basu *et al.*, 2002, Deane *et al.*, 2004, Kultz, 2005, Iwama *et al.*, 2006, Deane and Woo, 2011, Currie and Schulte, 2014, Nakano, 2016, 2020, 2021a, Hochachka and Somero, 2002, Sopinka *et al.*, 2016). Accordingly, the levels of catecholamines, cortisol, and glucose in blood and HSPs in tissues are most widely used for monitoring stress in fish (Barton and Iwama, 1991, Iwama *et al.*, 2006, Nakano, 2020, 2021a, 2021b, Sopinka *et al.*, 2016). However, most conventional methods for measuring stress, which employ anesthesia or tissue sampling by dissection, induce physical restraints. Recently, a new biosensor immobilized with glucose oxidase has been developed to measure blood glucose levels (Wu *et al.*, 2015, Wu *et al.*, 2019). This biosensor can nondestructively and noninvasively measure blood glucose levels in fish while swimming. Hence, this biosensor system could be useful for rapid, reliable, and convenient analysis of fish stress.

The stress response of the organism is an adaptation process that uses various functions of the whole body to deal with stress. Many reactions in organisms seem to be built on a delicate balance of anti-stress (defensive process) and stress (offensive process) responses. Hence, if this delicate balance in organisms is lost, the organisms will eventually fall ill (Nakano, 2016, 2021a).

3. Effect of environmental stressors on fish health

3.1 Stress-related biomarker expressions upon heat stress

The physiological states of fish depend on the environmental temperature. Heat shock can lead to many kinds of changes in biological functions. Daily and seasonal temperature changes have an impact during the life of individual fish (Basu *et al.*, 2002, Iwama *et al.*, 2006, Currie and Schulte, 2014). However, studies on the heat shock response in fish have primarily focused on the expression and characterization of HSPs as mentioned above (Iwama *et al.*, 1998, Iwama *et al.*, 1999, Basu *et al.*, 2001, Basu *et al.*, 2002, Deane *et al.*, 2004, Iwama *et al.*, 2004, Iwama *et al.*, 2006, Currie and Schulte, 2014, Nakano, 2020, Schreck and Tort, 2016, Sneddon *et al.*, 2016, Sopinka *et al.*, 2016). The changes in the levels of redox-related biomarkers, such as glutathione (GSH) and lipid peroxide (LPO), in response to heat shock have been reported for coho salmon (*Oncorhynchus kisutch*), cold water fish species and one of the most valued aquaculture species (Nakano *et al.*, 2014). The LPO levels in the plasma of stressed fish gradually increased after heat treatment. The total GSH levels in plasma temporarily decreased, but they returned to the basal levels by 17.5 h post-stress. The activities of superoxide dismutase (SOD), an important antioxidant enzyme, in the plasma of stressed fish increased significantly at 17.5 h post-stress compared with those in control fish, but returned to the basal levels at 48 h post-stress. The expression levels of hepatic GSH and HSP70 gradually increased after heat treatment. Similar changes in the levels of stress-related biomarkers in response to heat shock have been also observed in tropical rabbitfish (*Siganus guttatus*) (Nakano *et al.*, 2011). The levels of stress-related markers in coho salmon were changed by thermal stress at the initial stage of heat treatment at 19℃, which was different from the reaction of rabbitfish. In rabbitfish, the expressions of stress-related markers by thermal stress took time and were changed at the later stage of heat treatment even at 34℃. Accordingly, the susceptibility to thermal stress might depend on several factors, such as fish species, breeding environment and life history. Cold water fish species such as coho salmon seem to be more susceptible to thermal stress, compared with

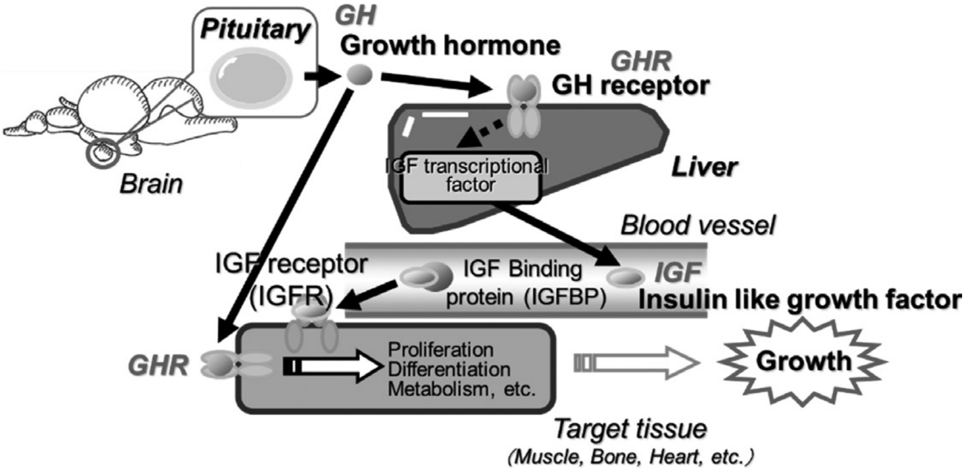

Fig. 2 Regulation of growth in fish. Growth in vertebrate including fish is regulated by the growth hormone (GH) secreted from pituitary gland and insulin-like growth factor (IGF) secreted from liver. The system responsible for regulation of growth in fish is called the GH-IGF axis. Growth is often influenced by a complex set of cellular, endocrine, and environmental factors.

tropical fish such as rabbitfish.

3.2 Stress-related biomarker expressions upon treatment with oxytetracycline

Oxytetracycline (OTC) is a broad-spectrum antibiotic (tetracycline family) with a bacteriostatic action against various gram-positive and gram-negative bacteria (Burridge *et al.*, 2010, Zounkova *et al.*, 2011, Yonar, 2012). OTC is the antibiotic at the first choice to treat many bacterial diseases in farmed fish (Burridge *et al.*, 2010, Yonar, 2012). However, high doses of OTC are known to cause side effects in fish and have detrimental effects on the environment. The expression of the stress-related biomarkers, such as GSH and HSP, in response to excessive doses of dietary OTC were determined for coho salmon (Nakano *et al.*, 2018, 2022). The GSH levels in the liver, muscle, and stomach in OTC-fed fish were higher than those in OTC-unfed control fish. Plasma GSH levels in the OTC-fed fish were also higher than those in the control fish. Expression levels of HSP70 in liver, muscle, and stomach decreased following OTC administration. The OTC concentration in the tissues of the OTC-fed fish, such as coho salmon, has been reported to accumulate in the order of stomach > liver > skin > muscle at the end of the OTC feeding period for 42 days (Rogstad *et al.*, 1991, Namdari *et al.*, 1996).

Heat shock-induced thermal stress and OTC treatment are known to enhance the production of reactive oxygen species (ROS) in various tissuess (Petrenko *et al.*, 1995, Lesser, 2006, Ho *et al.*, 2013). Accordingly, the changes in the levels of multiple stress- and redox-related biomarkers observed in the above-mentioned studies suggest that thermal and chemical stressors might induce oxidative stress in fish (Kaur *et al.*, 2014, Nakano, 2020, Nakano *et al.*, 2018, 2022, Nakano and Wiegertjes, 2020).

3.3 Growth-related gene expressions upon physiological stress

As shown in Fig. 2, growth in fish is regulated to a large extent by growth-related systems, such as the liver-derived insulin-like growth factor (IGF)-1 in response to the binding of pituitary-secreted growth hormone (GH) to the GH receptor (GHR). The GH-IGF-1 axis in fish has a critical role in regulating growth (DEANE and WOO, 2009, REINECK, 2010, NAKANO, 2016, 2021). Coho salmon showed the changes in mRNA expression levels of *gh*, *ghr*, and *igf1* genes in response to acute physiological stress derived from a 2 min of chasing in the tank by a hand-held dip net followed by a 0.5 min aerial exposure after scooping with the dip net (NAKANO *et al.*, 2013). After exposure to handling stress, the mRNA levels of hepatic *igf1* transiently increased, then decreased 16 h post-stress, whereas those of *ghr* in the pituitary, liver, and muscle decreased gradually in response to the stress. However, the pituitary *gh* mRNA levels did not change during the treatment. These observations indicate that *gh*, *ghr*, and *igf1* responded differently to the stress. An acute physiological stress could mainly down-regulate the expressions of *ghr* and *igf1* in coho salmon. These results also suggest that neuroendocrine substances, such as cortisol and catecholamines, participate in stress response.

4. Eustress in farmed fish

It is thought that chronic stress accelerates aging and functional disorder of tissues, and that oxidative stress-induced damage plays an important role in this process. The physiological stress is often interpreted as having a negative impact on health. In fact, stress generally creates negative effects as we know. However, it has been recently suggested possible for animals and plants to manipulate eustress (positive or desirable stress) and to avoid distress (negative or undesirable stress) (NIKI, 2007, OKEGBE *et al.*, 2012, HIDEG *et al.*, 2013, KUPRIYANOV and ZHDANOV, 2014, AFONSO, 2020, YAMAUCHI and SUTO, 2022 NOAKES and JONES, 2016, SCHRECK and TORT, 2016, SNEDDON *et al.*, 2016). When the organism is exposed to stressors that induce distress, a functional physiological state is no longer maintained. However, when the organism is exposed to stressors that induce eustress, it acquires a qualitatively different physiological state, while it still maintains homeostasis. The eustress is one of the hormesis effects of toxicants: the toxicant has a benefit on the organism when it ingests under a certain threshold concentration, but the excessive amount of the toxicant becomes toxic on the organism (NIKI, 2007). It is known that ROS-induced severe oxidative stress leads to oxidative damage *in vivo*. However, a moderate level of oxidative stress promotes altered cellular functions, giving rise to benefits on animal health (MILISAV *et al.*, 2012, GORRINI *et al.*, 2013).

It is thought that the redox balance in fish exposed to various environmental stressors, such as heat shock and antibiotics, is shifted to the oxidizing direction, which may induce oxidative stress *in vivo* (NAKANO *et al.*, 1999, KAUR *et al.*, 2014, NAKANO *et al.*, 2014, NAKANO *et al.*, 2018, 2022, NAKANO, 2020, NAKANO *et al.*, 2020, NAKANO and WIEGERTJES, 2020). Many stresses derived from various environmental stressors are those of oxidative, suggesting that the antioxidants are effective as an antistress supplement to cope with the environmental stress (NAKANO and WIEGERTJES, 2020, NAKANO, 2020, 2021a, 2021b). Accordingly, manipulation of controlled stress treatment, such as mild physiological or thermal treatment, and use of adequate concentrations of antioxidative supplements could be employed as eustresses to improve the health of farmed fish (Fig. 3) (NAKANO *et al.*, 1995, NAKANO *et al.*, 1999,

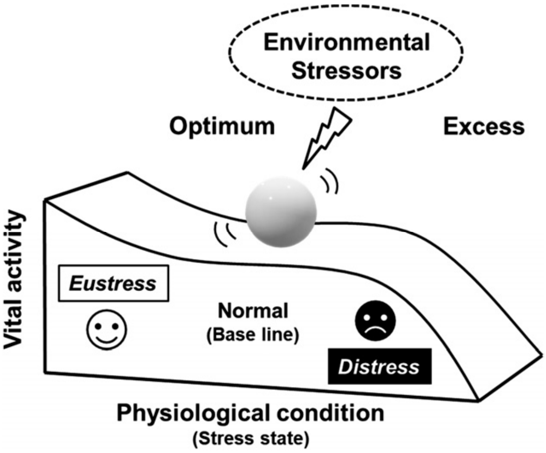

Fig. 3 Schematic view of altered physiological conditions with different stress states in response to environmental stressors in fish body. The physiological condition of fish body is like a ball. Environmental stressors can affect the condition and vital activity of fish body.

Nakano *et al.*, 1999, Nakano *et al.*, 2004, Niki, 2007, Deane and Woo, 2009, Okegbe *et al.*, 2012, Nakano *et al.*, 2013, Nakano *et al.*, 2014, Wu *et al.*, 2015, Nakano *et al.*, 2018, Afonso, 2020, Nakano, 2020, Nakano and Wiegertjes, 2020, Cerqueira *et al.*, 2021, Schreck and Tort, 2016, Sneddon *et al.*, 2016).

5. Conclusions and perspective

Aquaculture is thought to be the fastest growing food production technology in the world. Aquacultural production will continue to grow rapidly (Froehlich *et al.* 2018, Garlock *et al.*, 2019). Seafood contains various kinds of health-related functional components that are rare in land-based animal and plant foods. Hence, seafood is believed to contribute to global food and nutrition security (Golden *et al.*, 2016, Hicks *et al.*, 2019, Costello *et al.*, 2020). Although the sources of stress in aquaculture are variable, it has been found that most of them induced in fish is oxidative (Nakano, 2016, 2020, Nakano *et al.*, 2018, 2022, Nakano and Wiegertjes, 2020, Nakano, 2021a). When fish falls ill due to stress, it is often difficult for the fish to be completely cured, and the quality and the value of the product derived from the fish are decreased. Not only routine management but also adequate and time-consuming treatment to cope with detrimental effects of stresses are required for farmed fish. The concept to employ eustress in aquaculture has the potential to provide innovative technology to keep fish health and to establish fish welfare (Conte, 2004, Bergqvist and Gunnarsson, 2013, Schreck and Tort, 2016, Sneddon *et al.*, 2016, Afonso, 2020, Barreto *et al.*, 2021, Franks *et al.*, 2021, Nakano, 2021, Yamauchi and Suto, 2022). Additionally, there is a line of increasing evidence that aquaculture-based food contributes to a more environmentally sustainable production of animal proteins, compared with that of land-based livestock animals (Nagasaki, 1996, Froehlich *et al.* 2018, Garlock *et al.*, 2019). Increased aquaculture production is important to supply animal proteins on a global scale. Aquaculture is known to require less feed crops and land space referring to country-level aquatic and terrestrial data (Nagasaki, 1996, Froehlich *et al.*, 2018). Aquaculture-based food production is expected, therefore, to contribute to the achievement of the United Nations' Sustainable Development Goals (SDGs) and the blue revolution (Froehlich *et al.* 2018, Garlock *et al.*, 2019, Costello *et al.*, 2020, Farmery *et al.*, 2021, Jacob-John *et al.*, 2021).

Further studies will reveal the contribution of stress management including eustress and distress to the promotion of health and welfare of farmed fish and the improvement of aquaculture system.

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