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The Endocrine Response to Stress - A Comparative View

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1. Introduction

1.1 The stress concept

The word stress is used extensively to name a situation of tension that can be applied to living organisms such as animals or plants but also to ecosystems or in geological phenomena. Nevertheless, the concept of biological stress is closely connected to the historic development of the meaning of this word by Hans Selye after his short paper in Nature (Selye, 1936), following a first approach by Walter Cannon who restricted the physiological changes of stress and injuries to the effects of catecholamines and the adrenal medulla. Other key contributions of Selye to the stress associated concepts were the word stressor, meaning the agent causing stress effects and the non-specificity of the neuroendocrine response, even after positive or negative stressors (Szabo, 1998). Being such a general and widely used concept, the term stress has received many definitions, some of them trying to characterize the phenomenon, others focusing the elicited response and others even including the types of stressors, i.e. symbolic or real (physical, chemical, pathogenic). Nevertheless, in all of them some key elements are included: A source or stressor, the non-specific reaction and the neuroendocrine response.

As a relevant physiological mechanism, the stress response by itself is not inherently bad. For example, glucocorticoids are released in animals in response to situations that are not normally regarded as stressful, including courtship, copulation and hunting. In addition, hormones which increase during stress periods, are also part of the reproductive process and induce hormonal cascades causing parturition in some species (Möestl and Palme, 2002). As an example, brine shrimp *Artemia* exposed under gnotobiotic conditions to a non-lethal heat shock increases the expression of Heat Shock Protein-70 (HSP-70), thus inducing a non-specific molecular stress response. When Artemia was challenged with pathogenic bacteria, *Vibrio campbellii* and *Vibrio proteolyticus*, a cross-protection against pathogens was observed if an appropriate combination of heat application and recovery treatment was applied (Sung et al., 2007).

1.2 Stress, a general phenomenon in living organisms

The overall stress response, meaning the array of reactions generated in most body compartments as a result of the threat of the stressor, is common to all organisms. The fight-or-fight response and the fear reactions can be seen as a common behavior from

invertebrates to man and the necessary energetic supply and coordination of neural circuits for these reactions are also common patterns among animals along the phylogenetic tree. Nonetheless, evolutive ancient organisms are also sharing some of the basic responses that are seen in lower vertebrates and mammals, for instance, heat shock protein expression or the increase of antioxidant enzymes.

Stress responses have been also described in microorganisms. It has been shown that mitogen-activated protein kinase (MAPK) cascades play an important role in transducing environmental threats to transcriptional machinery by means of phosphorilation and regulation of several key transcription factors (Karin, 1998). Although it is well known that these cascades are activated by hormones or cytokines in vertebrates, stressors such as anoxia, osmotic shock or radiation may also induce this activation. In bacteria such responses have been detected as well as the heat shock response. Thus, in *Escherichia coli* it has been shown that transcription factors recognize specific heat-shock promoters, and that in most bacteria the control of major Heat-Shock genes is highly regulated (Segal and Ron, 1998). In fungi, it has been observed that stress originated from nutrient deprivation causes debilitation of fungal propagules, autolysis, inhibition of spores and loss of pathogenic aggressiveness (Hyakumachi and Arora 1998). This is another common aspect of the stress reaction response, i.e. the consequences derived from energy depletion that can be mirrored with the higher vertebrate stress responses. Thus, all these changes are related to a reorganization of metabolic and energetic pathways to face the effects of the stressor, a mechanism that is essentially the same type of stress response in higher vertebrates and mammals.

The stress concept has also been applied to plants when facing unfavorable environment or constriction of nutrients, water or inadequate soil conditions and a significant amount of scientific literature is available concerning plant stress, mostly related to unfavorable or changing environmental conditions. In plants, a multitude of stressors with different modes of action elicit very similar non-specific responses, besides those specific ones related to the particular stressor. Larcher (1987) defined the stress response in plants as the state in which increasing demands made upon a plant lead to an initial destabilization of functions followed by normalization and improved resistance. Lichtenthaler (1984) extended the stress concept in plants by including regeneration and differentiating between eustress (activating and stimulating positive elements for plant development) and distress (severe stress that affects negatively the plant, causing damage), concepts that have been used also in animals. Plants have a centralized system of stress response that enables to develop physiological responses and this has been shown to work under low-resource environments such as deserts, shaded understory or infertile soils. This response includes slow growth, low synthetic rate (photosynthesis) and low nutrient uptake. As in animals, these responses are driven by hormones and include changes in their balance, for instance producing more abscisic acid and often cytokinins. Thus, there is now strong evidence that the plant hormone abscisic acid (ABA) plays an important role in the regulation of drought stress, since a plant can use the ABA signalling mechanism and other chemical signals to adjust the amount of water loss in response to changes in both the rhizospheric and the aerial environment. This hormone will work as an equivalent of renal hormones of animals after environmental stress. Another example is the biotic stress that induces changes in hormone synthesis and hormonal signalling cascades in the auxin, gibberellin, ABA, ethylene and jasmonate pathways, and in addition modifying plant defense mechanisms, some of them associated to the ubiquitin/proteasome system, a similar pathway that is found in vertebrates (Wilkinson and Davies, 2002).

2. The stress response

The stress response in vertebrates has been defined following the model proposed in mammals by Selye. Together with the conserved cellular response, some other common elements such as the non-specific neuroendocrine activation and the interaction between regulatory systems, are also observed in non-mammalian vertebrates.

2.1 Molecular and cellular responses

Cells encounter a range of physiological and environmental stresses that require adaptive changes in gene expression. Stress conditions include ultraviolet (UV) irradiation, temperature changes, nutrient limitation, oxidative stress, hypoxia and exposure to various drugs or toxins. Exposure of cells to stress elicits adaptive responses that require the coordinated expression of stress-response genes, which affect cell survival, apoptosis, cell-cycle progression and differentiation (Holcik and Sonenberg 2005). The cell stress response assesses and counteracts stress-induced damage, temporarily increases tolerance to such damage, and/or removes terminally damaged cells by programmed cell death (apoptosis). The capacity of the response depends on the proteome expressed in a cell at a particular time and is therefore species- and cell type-dependent (Kultz, 2005).

One of the major cell stressors is the oxygen radical. Although the concept of endogenous oxidants was at first controversial, the identification of superoxide dismutase (SOD), an enzyme whose main function is the removal of superoxide anions, involved that oxygen radicals are main stressors for the cells and that removal mechanisms are stimulated to reduce adverse effects. In terms of aging it was also proposed that higher metabolism and elevated use of oxygen involve protein and cell damage and overall life reduction at longer term. Given that mitochondria produce most of the energy in the cell, and correspondingly consume the bulk of intracellular oxygen, the free-radical theory of ageing supports the hypothesis that the higher the metabolic rate of an organism, the greater the production of reactive oxygen species (ROS) and hence the shorter the life span. In this way, studies on reactive oxygen species related to aging have determined a number of key molecules that are regulating common mechanisms in organisms, from invertebrates to humans. For instance, work done in a model organism, the worm *Caenorhabditis elegans* has determined that the forkhead transcription factor, DAF-16, seems to be in a central position to integrate a variety of signals induced by stress and the nutritional status, such as MAPK pathways (through JNK-1), insulin (through DAF-2) and steroid hormone signalling through DAF-12 (Dawson & Dawson 2003). Moreover, insulin and insulin/IGF signalling may not only be involved in the regulation of oxidative stress response and longevity, but also it is quite likely that they may have a role in other degenerative disease mechanisms involving cellular stress. (Baumeister et al., 2006).

However, in some species the strict correlation between metabolic rate and life span is not maintained and this would depend on the production rate of reactive oxygen species combined with the prevention mechanisms that avoid this production. This is particularly true for birds and primates, who tend to live longer than would be predicted by their metabolic rates. Careful analysis of oxidative production rates demonstrated that at a given metabolic rate, mitochondria from these species tend to produce fewer ROS. (Finkel and Holbrooke, 2000). This indicates that ROS production rather than metabolic rate provides the strongest correlation with overall longevity. Another consequence, in terms of stress regulation in cells, is that under situations of metabolic stress, mitochondrial oxidant

products seem to function as signalling molecules (Finkel and Holbrooke, 2000). Therefore, stress episodes involving a rise in intracellular oxidant levels have three important effects: damage to various cell components, triggering of the activation of specific signalling pathways and development of mechanisms reducing ROS production.

Another of the cell responses to stress is selective translation as it has been shown that this event commonly occurs during cellular stress and during apoptosis. Moreover, global translation is reduced in response to most types of cellular stress. This results in savings of cellular energy, which is mainly consumed in the process of translation, estimated as an average of about 50% of the cellular energetic resources. Remarkably, the stress-induced attenuation of global translation is often accompanied by a switch towards the upregulation of the selective translation of proteins that are required for cell survival under stress (Holcik and Sonenberg 2005).

Another key aspect of the cell response is the modulation of major pathways of energy metabolism, closely linked to the oxidative burst in stressed cells. Selected enzymes related to energetic pathways contribute strongly to the control of key pathways such as glycolysis, pentose phosphate pathway, and the citrate cycle. Induction of these enzymes during stress may be necessary for generating reducing equivalents (NADH, NADPH) that are needed for cellular antioxidant systems. In this way, a number of key enzymes such as the enzyme Enolase have been shown to be highly induced under different types of potential stressors. Thus, in vertebrates Enolase is expressed in most tissues as a response to either physical or chemical stressors, pathogens or immune stimuli and even under pathogenic states such as cancer. As it is a key enzyme of the glycolytic pathway, the role of this enzyme appears to be relevant in switching the energetic flows under any type of stress source (Ribas et al.,2004).

Regarding cellular responses to stressors, heat shock proteins (Hsp) are considered one of the main cell mechanisms responding against stressors. Stressors disturb cellular homeostasis and induce a corresponding homeostatic response of these proteins that in most cases have the characteristic of being permanent until environmental conditions change again, and that are triggered by stressor-specific sensors that monitor specific environmental variables. Hsp are a defined set of proteins that are conserved along evolution and perform protective cellular functions such as cell cycle control, protein chaperoning and repair, DNA and chromatin stabilization and repair, or removal of damaged proteins. Thus, from a number of 300 common proteins that have been identified in many organisms from human to yeast or bacteria, about 40 of them are involved in the cell response to stress. This response can occur via stressor-specific interactions, post-translational modifications, and fragmentation of stress proteins resulting in an induction of a common set of stress proteins triggered by molecular damage or oxidative accumulation (Kültz, 2005). In combination with the DNA repair machinery, molecular chaperones are required to recognize unfolded proteins and either target them for removal, stop their aggregation, or assist in their refolding into the native, functional state. These proteins are extensively utilized as bioindicators of environmental stress in many different types of organisms.

2.2 The integrated physiological response.

The stress response system in vertebrates has both central nervous system (CNS) and peripheral components. The central tissue components of the stress system in mammals are located in the hypothalamus and the Locus ceruleus in the brainstem, and include a number of endocrine messengers with a principal role in mediating the neuroendocrine stress response, being the CRH (Corticotrophin Releasing Hormone) the key peptide in this

activation. The roles of the related peptides, the urocortins, in stress responses are beginning to be understood in mammals, but very little is known about their expression and function in non mammalian species. Also, CRH and urocortins are expressed throughout the body where they may play diverse, but as yet poorly characterized, roles in tissue development and homeostasis (Denver, 2009). Another hypothalamic peptide, TRH (Thyrotropin Releasing Hormone) also has such activation properties in fish. These hypothalamic factors stimulate the release of the Adrenocorticotropic Hormone (ACTH) from the pituitary which in turn induces production and release of the major stress steroid, cortisol, by interrenal cells located within the head kidney (Tort, 2010).

The components of the stress system include the peripheral limbs of the hypothalamic-pituitary-adrenal (HPA) axis; the efferent sympathetic-adrenomedullary system; and components of the parasympathetic system. Given the potential for the convergence of these mechanisms, specifically in the nervous system, it may be suggested that interactions between the two systems would be produced already at the initial stages of corticosteroid signalling (Riedemann et al., 2010). In emergency situations, the hypothalamus is activated and stimulates the sympathetic nervous system and the adrenal medulla which releases adrenaline and noradrenalin, and the adrenal cortex which releases GCs. The effects are global, and the nerves as well as hormones stimulate the systems needed for fight-or-flight (it is usually a short duration stress response). These peripheral components may be limited to these former elements, or one could include other hormonal axes and structures that are stimulated by the neuroendocrine agents and that exert important actions on the whole metabolism and the overall energetics. These other peripheral components are considered below.

3. Comparative endocrine response to stress

Endocrine changes after stress are clearly observed in vertebrates where a common endocrine pattern can be recognized (see table 1). Nevertheless, invertebrates also experience changes in hormones after stressors. For instance, in crustaceans, the hyperglycemic hormone (CHH) from the lobster, *Homarus americanus* increases in hemolymph following emersion. Significant levels of hemolymph CHH have been also measured in lobsters that had been eyestalk-ablated and it has been observed that these animals continued to produce CHH, even though the main source of CHH had been removed, probably produced in other portions of the central nervous system (Chang et al., 1999). As another example, in arthropods, proteins of the hemocyanin gene family are involved in major physiological processes, including aerobic respiration, the innate immune response, and molting. Members of this hemocyanin family, cryptocyanin, and phenoloxidase, are multi-subunit molecules that assemble into hexamers and higher aggregates. The hemocyanin hexamer heterogeneity is maintained as a mechanism of selection for functional diversity under environmental stress when changing developmental and environmental conditions (Terwilliger et al., 2006), a similar response that can be observed in vertebrates related to specific endocrine or immune molecules.

3.1 Mammals

The stress response in the brain starts in the parvocellular neurons of corticotropin-releasing hormone (CRH); the arginine vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus; the CRH neurons of the paragigantocellular and parabranchial

	Fish	Amphibians	Reptiles	Birds	Mammals
Pituitary anatomy	Bigger pars intermedia Smaller median eminence	Bigger pars intermedia Smaller ventral lobe	Longer pars nervosa Bigger pars itermedia	Bigger ventral lobe Bigger median eminence Smaller pars intermedia	Bigger ventral lobe
Adrenal anatomy	Cells scattered in the head part of the kidney	Cells inside the kidney in islets (urodele) or strands (anuran)	Cells in lobular structures close to the gonads	Cells in lobular structures at top of the kidneys	Cells in lobular or irregular structures at top of the kidneys
Catecholamine	Adrenaline	Adrenaline	Adrenaline	Adrenaline and Noradrenalin	Adrenaline
Corticosteroid	Cortisol	Corticosterone	Corticosterone	Corticosterone	Cortisol or Corticosterone

Table 1. Details of the pituitary and adrenal anatomy and the main secretion, catecholamines and corticosteroids in vertebrates

nuclei of the medulla and the Locus ceruleus (LC); and other mostly noradrenergic (NE) cell groups in the medulla and pons (LC/NE system). The principal effectors include CRH, AVP, the proopiomelanocortin-derived peptides (POMC) α-melanocyte-stimulating hormone (MSH) and β-endorphin, the glucocorticoids (GC) and the catecholamines noradrenalin and adrenaline. Signalling by CRH-like peptides is mediated by at least two distinct G protein-coupled receptors and modulated by a secreted binding protein. These neuropeptides function as hypophysiotropins and as neurotransmitters/ neuromodulators, influencing stress-related behaviors, such as anxiety and fear. In addition to modulating HPA activity and behavioral stress responses, CRH-like peptides are implicated in timing key life history transitions, such as metamorphosis in amphibians and birth in mammals. CRH-like peptides and signalling components are also expressed outside of the central nervous system where they have diverse physiological functions (Denver, 2009).

In mammals, the adrenal gland, also known as the suprarenal gland, is a two-paired gland, yellow- or orange-colored, triangle-shaped, located over the superior part of the kidney, one on each side. The adrenals are mainly responsible for regulating the response to stress through the synthesis of catecholamines and corticosteroid hormones. In other vertebrates, this gland is also associated with kidneys but its anatomical arrangement is different, as it will be described latter on this chapter. In mammals, the adrenals have a distinct outer-cortex and inner-medulla arrangement, which is characteristic of this group of vertebrates. The adrenal medulla occupies the central part of each adrenal gland and accounts for 22% of the gland weight; the remaining 78% of the weight corresponds to the adrenal cortex and adrenal capsule that surrounds the gland. Both the adrenal medulla and cortex receive regulatory input from the nervous system (Binkley, 1995).

The central region (medulla) of the adrenal gland, have specific cells called chromaffin cells, which are considered modified postganglionic cells of the sympathetic nervous system. These chromaffin cells secrete catecholamines, adrenaline (or epinephrine), noradrenalin (or norepinephrine) and to a lesser extent, dopamine. The mammalian adrenal cortex can be divided into three layers: zona glomerulosa, zona fasciculata and zona reticularis; all three layers produce corticosterone, but otherwise, the layers are specialized as regards their main

hormone products. Briefly, the zona glomerulosa, which represent about 15% of the adrenal weight, is the outer layer and is specialized in production of aldosterone. The zona fasciculata is the central and widest layer of the adrenal cortex (around 50% of adrenal weight) and secretes cortisol and androgens. Finally, the zona reticularis, represents 10% of the adrenal weight, secrete cortisol and androgens. These two last zones respond to ACTH stimulation.

In an initial alarm phase, catecholamines are released into the circulatory system, where they circulate in a free form or conjugated to blood proteins; in blood, catecholamines have a short half-life of about 3 to 4 minutes. Its biosynthetic pathway of synthesis is highly conserved throughout the animal kingdom with the rate-limiting step controlled by the enzyme tyrosine hydroxylase (Perry and Capaldo, 2010). Both catecholamines have a large number of actions, most of which contribute to the sympathetic fight-or-flight response. The best well known functions of adrenaline and noradrenalin are their actions in the cardiovascular system, the stimulation of glycogenolysis in skeletal and cardiac muscle, mobilizing glucose in those tissues, which aimed at reducing the detrimental effects of stressors on physiological function or optimizing physiological processes during periods of increased energetic demand. In the more highly evolved vertebrates, such as mammals and birds, the acute humoral adrenergic stress response effectively complements the neuronal regulation of physiological systems via the sympathetic division of the autonomic nervous system (Perry and Capaldo, 2010).

Cells of adrenal cortex respond to the HPA axis and mediate the stress response through production of steroid hormones, namely mineralocorticoids and GCs. The HPA axis involves the release of corticotropin releasing hormone (CRH) and Vasopressin from hypothalamic PVN, and CRH is the main responsible for stimulating adrenocorticotropic hormone (ACTH) release from the anterior pituitary gland. ACTH arrives at the target cells in the adrenal cortex where it stimulates the synthesis of GCs. In humans, monkeys, sheep and cats cortisol is predominantly secreted; whereas rodents mainly secrete corticosterone. Some other mammals, such as dogs, secrete a mixture of cortisol and corticosterone in a similar ratio (Boonstra, 2004). GCs act at multiple sites within the body in an attempt to maintain homeostasis, but because of the potential damaging effects of chronic exposure to GCs, the HPA axis is tightly regulated through classic negative feedback loops. Thus, cortisol feeds back on hypothalamus and pituitary to cause rapid inhibition of CRH release. Under acute stress conditions, feedback mechanisms are efficient and the system returns to normal, resulting in short-term effects on body processes. Under conditions of chronic stress, feedback signals are weak and the system remains activated for longer periods, resulting in effects on body processes that can be long term and detrimental (Boonstra et al., 2004).

After short-term stressors, cortisol affects the intermediary metabolism by stimulating gluconeogenesis in liver, increasing glycogen formation and increasing the availability of substrates derived from proteins and fats. All these actions tend to produce hyperglycemia, increasing the availability of quick energy to muscle and nervous tissue. Chronic or repeated exposure to a stressor, characterized by lower but prolonged endocrine secretions, often involve longer recovery periods and much higher energetic and performance costs, due to both stressor persistence and the derived effects of the stress response effectors, i.e., GCs. These negative effects include alterations at several physiological levels, from impaired growth and reproductive capacity to immune suppression (Tort, 2010).

3.2 Birds

In birds adrenal glands may be a single median structure or two separate organs, in close contact with each other, lying just cranial to the kidneys and gonads on either side of the aorta and caudal vena cava. The adrenals are small, ovoid in form, with a yellow or orange color, and are surrounded by a loose connective capsule. In contrast to mammals, the cortex is not well differentiated from the medulla. Clusters of chromaffin cells are mixed with blood vessels and the interrenal steroidogenic cells are radially arranged in the subcapsular zone and in the inner part of the gland (reviewed by Ghosh et al., 2001).

Adrenaline and noradrenalin are secreted by the medullary part of the gland and unlike in mammals, the enzyme PNMT exists in all adrenomedullary chromaffin cells, so it cannot be considered a marker in differentiating adrenaline from noradrenalin cells. PNMT exists in its active form only in the adrenaline-storing cells (Ghosh et al., 2001). The chromaffin cells are usually mixed and arranged without any preferential location, but unlike most other vertebrate groups, there is strong inter-specific variation in the noradrenalin/adrenaline cell ratio (Varano, 1980). This ratio seems to bear a distinct relation to avian phylogeny; thus, less evolved birds have more noradrenalin, while recently evolved birds have more adrenaline. In these terms, birds occupy an intermediate evolutionary position having noradrenalin/adrenaline ratios around 1/1 (Ghosh, 1977; Varano, 1980).

The most important glucocorticoid in birds is corticosterone, which is secreted by the cortical part of the gland and has both glucocorticoid and mineralocorticoid activity, having a more important role than aldosterone in electrolyte balance. In general, birds have low basal circulating corticosteroids levels, but these levels increase during stress-related responses as occurs in mammals (Boonstra et al., 2004). The acute short action stress response (fight or flight) is activated within seconds by the sympathetic nervous system which induces release of catecholamines from chromaffin cells of the adrenal medulla into the general circulation and release of CRH primarily from the hypothalamus, which induces ACTH secretion from the anterior pituitary and, in response to ACTH, release of corticosterone into the general circulation within minutes.

Ghosh and collaborators (2001) demonstrated that catecholamines cause hepatic and muscle glycogenolysis which can lead to hyperglycemia, as it occurs in mammals. The avian adrenal chromaffin tissue is influenced by the steroidogenic cells; GCs increase noradrenalin content in the chick and adrenaline content in the pigeon adrenal glands, with a synergistic action requiring activity of the splanchnic nerve (Ghosh et al., 2001). Compared to mammals, less is known about the effects of catecholamines on bird metabolism. Starvation experiments on birds of different food habits demonstrated a simultaneous depletion and release of catecholamines and glycogen.

3.3 Reptiles

In reptiles, the adrenal glands are discrete bodies; yellow/red in color, separated from the kidneys, and in close relationship with the gonads, lying in its dorsal part. The only exception to this pattern is in the chelonians where the adrenal gland is in close contact with the ventral surface of the kidney, as in anuran amphibians. Chelonians have dorsoventrally glands which lie against the kidney. Ventrally, they are covered by peritoneum that extends forward to form the mesorchium or mesovarium of the adjacent gonads. Snakes and lizards have adrenal glands incorporated into the mesorchium or mesovarium, close to their respective gonads. They are elongated in snakes and usually globular in lizards. The right gland is attached to the caudal vena cava (reviewed by Perry and Capaldo, 2010).

The chromaffin and the steroidogenic tissues are associated, but there is a substantial variation in the degree of mixing that depends on the considered group. Thus, in Crocodilians and Chelonians, chromaffin and steroidogenic tissues are largely intermingled. In Rincocephalian lizards, most of the chromaffin tissue forms a dorsal mass that send extensions between the interrenal cells; moreover, many clusters of chromaffin cells are present within the steroidogenic parenchyma, and some clusters of chromaffin cells are present on the ventral surface of the gland. Most Squamata lizards or iguanas show a similar distribution, with the exception of the ventral chromaffin tissue, usually absent in these reptiles (reviewed by Perry and Capaldo, 2010). Moreover, the distribution of the two tissues presents a great variability, which is correlated to the phylogeny of the species. Generally, a high degree of separation between the two tissues is typical of ancient species, whereas a trend toward the close association between them is typical of more recent species (Laforgia et al., 1991).

The distribution of noradrenalin and adrenaline cells is different among groups of reptiles. Usually, the islets intermingled in the steroidogenic parenchyma are occupied only by adrenaline cells, whereas noradrenalin and adrenaline cells are present in the chromaffin superficial tissue. In reptiles, the ratio between noradrenalin/adrenaline reflects the degree of separation between steroidogenic and chromaffin tissues. Thus, high values of this ratio, and therefore a high number of noradrenalin cells, correspond to a high degree of separation of the two tissues whereas low values of this ratio, correspond to a high degree of mixing between them. The reason for this correspondence, as it has been clarified by Perry and Capaldo (2010), is that in reptiles and mammals, the enzyme PNMT, that catalyses the methylation of noradrenalin into adrenaline, is activated by GCs. Therefore, when the two tissues are spatially separated, GC delivery to the chromaffin cells is likely to be impeded, whereas, when the degree of integration is high, GC delivery to the chromaffin cells is likely to be facilitated.

In response to stress, reptiles produce different patterns of catecholamine release, which can increase or decrease according to the type of stressor. For example, restraint stress in alligators causes a decrease in plasma adrenaline and noradrenalin levels at 24 h, and an increase in noradrenalin levels by 48 h. The role of catecholamines in regulating reptilian metabolism is poorly studied although it is clear that adrenaline causes hyperglycemia and promotes glycogenolysis in liver and glycogen deposition (Norris, 2007).

Corticosterone is the major adrenal corticosteroid secreted by reptiles (see Tyrrel and Cree, 1998) but the patterns of basal corticosterone secretion vary considerably among them. However, almost all studies concerning the HPA modulation by stressors show that reptiles respond to stressors by increasing plasma levels of corticosterone (Tyrrel and Cree, 1998; Moore and Jessop, 2003). Nonetheless, it is evident a variation in the rate, duration and magnitude of the adrenocortical response to the same type of stressor, reflecting a change in the sensitivity of the HPA axis to stressors (Wingfield and Romero, 2001). A number of studies have demonstrated that differences in physiological state among individuals, such as body condition, reproductive state, disease status, age, sex, genotypic variation, and social status can result in adrenocortical modulation (Dunlap and Schall, 1995). In addition, differences in external environment such as variation in rainfall, temperature, food availability, and humidity or general habitat quality can result in individual adrenocortical modulation between populations (Moore et al., 2001).

3.4 Amphibians

The adrenal glands of amphibians are found in close association with the kidneys, although their exact location varies with the species. Like reptiles and birds, the adrenal gland

appears homogenous on cut surface, and histologically it is comprised of intermingled cortical and medullary elements, rather than having the clear delineation between cortex and medulla seen in mammalian species. Thus, in amphibians the chromaffin cells are closely associated with the steroidogenic cells; additionally, chromaffin cells can be found in the extra-adrenal chromaffin tissue, within the paravertebral sympathetic ganglia and in the abdominal para-aortic region, but their precise role at these sites is not well understood. The arrangement of adrenal chromaffin cells is markedly different in anurans and urodeles (Accordi, 1991; Chimenti and Accordi, 2008). In urodeles, the steroidogenic tissue forms numerous small bodies, partially embedded in the ventral surface of the kidney with groups of chromaffin cells interspersed (reviewed by Perry and Capaldo, 2010). In anurans, noradrenalin and adrenaline cells are usually intermingled, with no preferential distribution. The adrenal gland produces both catecholamines and corticosteroids (Wright 2001).

Amphibian chromaffin cells generally receive a scarce nerve supply and because of the tight intermingling between steroidogenic and chromaffin tissues, regulation of the chromaffin cell activity is likely achieved by paracrine interactions between the two tissues (Capaldo et al., 2008a, b). Amphibian chromaffin cells are regulated by multiple factors, including humoral agents carried from the blood stream, neurotransmitters and neuropeptides.

It is known that ACTH is one of the main regulators of steroidogenic tissue activity in amphibians (Norris, 2007; Sicard and Vaudry, 2000) and that corticosterone, the main corticosteroid secreted by amphibians, generally increase as a response to stress (reviewed by Moore et al., 2003). However despite the existence of adrenocortical modulation, there is little understanding of what physiological mechanisms operate within the HPA axis to enable modulation of corticosterone release during stress both in amphibians and in reptiles (Moore et al., 2001). A limited number of studies have documented the effects of stressors on the catecholamine release in amphibians. But, in general, stress situations such as hypoxia and forced exercise (Romero et al., 2004) elicit an increase in plasma catecholamines. Elevated catecholamine concentrations cause hyperglycemia via its stimulatory action on glycogenolysis in both liver and muscle (Norris, 2007).

Adaptation to an unfavorable environment can take place under very difficult conditions, as demonstrated in desert amphibians: tadpoles of these species can accelerate metamorphosis as their pond dries, with earlier birth of a more mature product, as long as an unfavorable larval environment is not experienced too early or too severely. Significant changes in the hormonal patterns are found under these circumstances. Similar adaptive phenomena are observed in humans involving elevation of corticosteroid secretion when fetal adverse circumstances are too severe. However, there is very likely a price to pay for this immediate beneficial effect on survival. Hippocampal damage could explain the high rate of learning disabilities and a number of diseases in adulthood (Amiel-Tison et al., 2004).

3.5 Fish

Although few studies have been undertaken in fish regarding the mechanisms and the neurophysiology of stress detection by the central nervous system (CNS) and sensory organs, the scheme of stress induced neuroactivation is similar than in other vertebrates. Stressors are detected and first processed in the CNS and then through neuroendocrine axis. In most species the Corticotropin Releasing Hormone or CRH-like activity has been found in the preoptic nucleus of the hypothalamus. The CRH travels to the pituitary where it

stimulates the corticotrope cells to release ACTH but in fish, it also stimulates the melanotropic cells to release α-Melanocyte-stimulating-hormone (α-MSH) and β-endorphin. Similarly, other peptides as TRH activates ACTH release and the HPI cascade. In the interrenal tissue of fish, ACTH is the main responsible for the cortisol release but other agents, like Angiotensin, Urotensin and Atrial Natriuretic Factor (ANF), may interact with ACTH in the cortisol secretion. It has also been shown that melanotroph products (α-MSH and β-Endorphin) may be important regulators of the corticosteroidogenesis and cortisol secretion.

In fish there is close association between adrenocortical and chromaffin tissue except in elasmobranch fishes where the tissues are completely separated and the adrenocortical tissue comprise a discrete gland which lies dorsally between the two posterior lobes of the kidney. The arrangement of chromaffin cells varies among the various groups of fishes along an evolutionary timeline. For example, in hagfish (Myxine) and lampreys (Lampetra), chromaffin cells are located within the heart (reviewed by Perry and Capaldo, 2010), as well as in the great veins returning blood to the heart (Gallo and Civinini, 2003). In teleost fish, the chromaffin cells are located within the walls of the posterior cardinal vein and in close association with the lymphoid tissue of the kidney. In general, chromaffin cells are often observed either singly or clustered into groups of several cells. The association of chromaffin cells with the steroidogenic interrenal cells may vary amongst different teleost species (Perry and Capaldo, 2010). Noradrenalin and adrenaline are the main catecholamines produced by fish chromaffin cells as it occurs in the other vertebrate groups. Noradrenalin and adrenaline producing cells can be distinguished on the basis of morphological characteristics. In teleost fish as in the other groups of fishes, the aminergic chromaffin and interrenal steroidogenic tissues form a diffuse organ at the anterior part of the kidney (called the head kidney), which is situated around the posterior cardinal vein and their branches (Gallo and Civini, 2004). Thus, the head kidney is the homolog to the adrenal gland, and is an organ of particular importance due to its cellular diversity and multiple functions associated (e.g. phagocytosis, hematopoiesis, catecholamine secretion by chromaffin cells, and cortisol secretion by interrenal cells).

Catecholamines, predominantly adrenaline, are released from chromaffin cells (Reid et al., 1998), immediately after stress. Once in the circulation, these hormones diminish the detrimental consequences frequently associated with stressful situations as in the other groups of vertebrates. Similarly, one of the primary roles of catecholamines is to modulate cardiovascular and respiratory function in order to maintain adequate levels of oxygen in the blood and, therefore, sufficient supply to the tissues mobilizing energy stores for the increased energy demands that often accompany stress (Perry and Wood, 1989; Randall and Perry, 1992 in Reid et al., 1998).

Activation of the hypothalamo-pituitary axis and release of ACTH into the circulation by the pituitary is also an integral part of the primary stress response of fish. ACTH stimulates the interrenal cells embedded in the kidney to synthesize and release cortisol into circulation for distribution to target tissues (Barton, 2002; Tort, 2010). The release of cortisol in teleostean and other bony fishes is delayed relative to catecholamine release. In fish, high plasma cortisol levels have a wide range of metabolic effects including, the modulation of carbohydrate metabolism through gluconeogenesis, increases in protein turnover, regulation of amino acid metabolism, ammonia output, glutamine synthetase and aminotransferase activity, and increased lipolysis (reviewed in Mommsen et al., 1999). Cortisol modulates the inflammatory response (Mackenzie et al., 2006; Aluru and Vijayan,

2009) and a range of other immune system responses (Maule and VanDerKooi, 1999), and appears to attenuate the cellular heat shock protein response to thermal insult (Ackerman et al., 2000; Basu et al., 2001 in Pankhurst 2010). Corticosteroid hormones also play a key role in osmoregulation (reviewed in McCormick, 1995), and are critical for controlling metabolism, hydromineral balance, and the overall stress response. Among corticosteroid hormones that have been well characterized in most vertebrate groups, the identity of one of the earliest vertebrate corticosteroid hormones, 11-deoxycortisol has been recently found in lampreys, a member of the agnathans that evolved more than 500 million years ago. This corticosteroid is regulated by the hypothalamus–pituitary axis and responds to acute stress (Close et al., 2010). This indicates that a complex and highly specific corticosteroid signalling pathway evolved at least 500 million years ago with the arrival of the earliest vertebrate, although it is assumed that this molecule may be derived also from an early ancestral corticosteroid receptor molecule (Thornton and Carroll, 2011).

Regarding the nuclear glucocorticoid receptor (GR), found in all vertebrates, it is known that in fish regulates cell growth, bone density, metabolism and modulates the cardiovascular system. Besides cortisol, also significant levels of 11-deoxycortisol and 11-deoxycorticosterone occur and these ligands bind to GRs and Mineralocorticoid receptors (MRs). It has been shown in fish that teleosts may have one or two different GR genes (Acerete et al., 2007; Bury et al. 2003). This discrepancy likely results from the fish specific genome duplication event. One of these two GR genes has two different transcripts that are generated by alternative splicing (Bury et al. 2003; Greenwood et al. 2003). Most interestingly, the three different GR forms in fish are differentially expressed in vivo and show different transactivational capacities, but only slightly different affinity for their ligand. As both genes and different splice variants are transcriptionally active, it is suggested that they both play an important and probably different role in the fish physiology (Bury et al. 2003, Greenwood et al. 2003). This multiple corticoid receptors in fish and a more complex signalling mechanism by related steroids provides an interesting model for comparative GR function (Stolte et al., 2006).

4. Consequences of the neuroendocrine activation

Response involving the sympatico-chromaffin axis, involves the activation of chromaffin tissue by specific neurons, resulting in the release of catecholamines, adrenalin and noradrenalin, which in turn induce the generation of large amounts of energy to meet the energetic needs of this active reaction. This is a very rapid response among all vertebrates and mainly involves the cardiovascular system. Regarding the HPA axis, a longer time is needed, since an endocrine cascade is activated and therefore the effects will be produced when the final hormone in the cascade, a corticosteroid has been released. Looking at the knowledge on comparative animal physiology, it can be sustained that the proteins, gene structures, and signalling pathways of the HPA axis are present in the earliest vertebrates and have been maintained by natural selection because of their critical adaptive roles. In all vertebrates so far studied, the HPA axis is activated as a response to stressors and is controlled centrally by peptides of the CRH family. It can be assumed that, irrespective of the behavioral or physiological outcomes, acute and chronic elevations of corticosteroid secretion initiate metabolic alterations and biochemical processes. Because of the dichotomy in the effects of acute and chronic GC responses, studies generally focus on either acute or chronic elevations of GCs (elevated basal values). When basal GC concentrations are

elevated, a common consequence is a weakening of the further acute GC response, probably through negative feedback mechanisms in the hypothalamic–pituitary-adrenal axis. This is an endocrine vicious circle: a chronically high baseline can provoke pathologies, and a weak acute response is ineffective at handling short-term stressors (Creel, 2001).

Since the energetic cost of the stress situation is high, it is clear that other hormone axes, mostly devoted to the metabolic support will have an influence on the immune function. Thus, the growth hormone and the somatotropic axis have also been shown to affect immune processes, and opioids and thyroid hormones have also been shown to modulate immune responses. The activation of catecholamines and corticosteroids induce a wide number of changes, in particular because these molecules have receptors in most tissues. Therefore, many if not all of the hormones involved in stress responses possess, in addition to their direct effects, induce pleiotropic or collateral consequences that may or may not reinforce direct or primary effect. These other effects can mediate the mechanisms that might affect other unrelated adaptive needs, as for example to modulate the responses of the cardiovascular system, osmotic equilibrium, disease resistance mechanisms and immunocompetence, energetic metabolism and reproduction (see Figure 1).

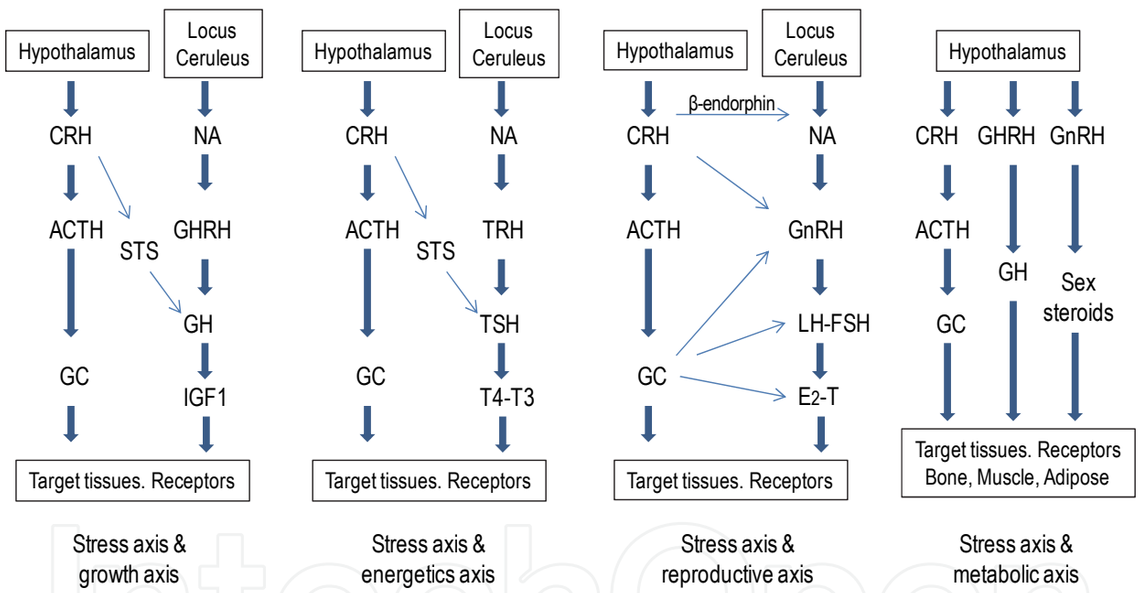

Fig. 1. Schematic diagrams of the endocrine interactions between the stress axis and growth, reproduction, energetics and metabolism

In terms of energetics and growth effects, stress generally shows depressive effects, inhibiting feeding behavior in all vertebrates. The effects of CRH on food intake are evolutionarily ancient, as this peptide inhibits feeding already in fishes, and the same effect is observed in birds and mammals. The effects of melanocortins on food intake have not been as extensively studied, but available evidence suggests that the anorexic role of neuronal melanocortins has been conserved. Data from mammals suggest an important role for hypothalamic neuropeptides, in particular the melanocortins and CRH-like peptides, in mediating stress-induced inhibition of feeding. Although there is evidence that CRH and the melanocortins influence hypothalamic circuitry controlling food intake, these peptides may have a more primitive role in modulating visuomotor pathways involved in the recognition

and acquisition of food. (Carr, 2002). Stress rapidly reduces visually guided prey-catching behavior in toads, an effect that can be mimicked by administration of CRH, while corticosterone and isoproterenol are without effect. Melanocortins also reduce prey oriented turning movements in amphibians and, in addition, facilitate the acquisition of habituation to a moving prey. The effects of these neuropeptides are rapid, occurring within 30 min after administration. By modulating visual and motor processing circuits these neuropeptides may help animals make appropriate behavioral decisions during stress episodes.

Many studies in the last decade have shown that stress can affect immune system both in mammals and lower vertebrates (Verburg-Van Kemenade et al., 2009; Dhabhar et al., 2009), although most of the reports are related to the effects of corticosteroids, and describe generally suppressive effects. Studies with human, murine and rat immune cells showed the immunosuppressive effects of elevated GC levels following stressful circumstances. GCs suppress Th1 cellular immunity and mediate a Th2 shift by suppressing production of T helper cells type 1/(Th1; tumor necrosis factor-a, interferon-g, interleukin-2 and interleukin -12 cytokines and inducing production of T helper cells type 1 (Elenkov 2004). Suppressive effects have been shown also in fish, where administration of cortisol induce a reduction of cytokine expression in cultured macrophages (Mackenzie et al., 2006; Castillo et al, 2009). Husbandry stressors applied to different species of fish result in a reduction of immunocompetence, showing decreased activity of immune response mechanisms (Montero et al., 1999), and reduction in efficiency after a combination of stress and pathogen treatment (Mauri et al., 2011).

Nevertheless, there are also episodes in which enhancement of immune function is observed, for instance during the immediate reaction, and this may depend on several considerations. One is the time-course, since acute or short-term stress often enhances innate and adaptive immune responses whereas chronic or long-term stress normally suppress or dysregulate immune function (Dhabhar et al., 2009; Tort, 2011). Another is the body compartment at which we are looking. Thus, skin is enriched with immune cells during acute stress, showing immuno-enhancement, while circulating blood may show depletion of leukocytes. A third factor may be the energetic situation of the animal since the demand of resources after stress are increased and they may be insufficient for other needs than facing the coping with stress itself. Whether there is an excess of demands and a shortage of energy resources, the immune system can be suppressed. Nevertheless, these arguments based on conservation of energy have been invoked to explain potential adaptive benefits of stress-induced immuno-suppression, but in one hand, some mechanisms for immuno-suppression expend, rather than conserve, energy. On the other hand, it can be also observed that while some immune responses are depressed or delayed, others are present without any decrease in efficiency, for instance, reducing the number of lymphocytes but increasing granulocytes . Therefore, the hypothesis is rather a temporal reorganization of immune resources than a pure suppression response. Maladaptive implications are present when stress becomes chronic; a situation that is unusual in nature and that evolution has yet to resolve (Dhabhar et al., 2009).

Stressors have been shown to reduce reproductive performance and, in lower vertebrates, even impair completely the reproductive process (Pottinger, 1999; Pankhurst 2009; Tort, 2011). In fact, the Hypothalamic-Pituitary-Gonadal axis and the Hypothalamic-Pituitary-Adrenal/Interrenal axis share a number of mediators, mainly steroid hormones. Therefore, stress and the activation of HPA axis affects the production of steroids. Interestingly, the

reproductive system can become resistant to inhibition by GCs in some reproductive contexts. For example, if GCs allocate resources away from reproduction, and thereby reduce individual fitness by impairing successful production of offspring, the benefit of the reproductive system ignoring the GC signal may outweigh the cost of not responding to the stressor. In salmon species and several marsupials, death occurs shortly after breeding. The proximate cause of death is the extremely high levels of GCs that catabolize essential proteins (Wingfield & Romero, 2001). Reproduction in these animals clearly continues despite elevated GCs. Furthermore, GCs do not inhibit reproduction in many short-lived species and in older individuals, and in dominant individuals in some species where the dominant individual has a limited period with access to mates (Wingfield & Sapolsky, 2003). Consequently, susceptibility to GC-induced inhibition of reproduction is highly specific depending on the importance of continuing reproduction in the presence of stress, which may vary depending upon age, sex or stage of the breeding cycle and of course, the species (Romero and Butler, 2007).

In the regulation of the stress response by steroid hormones it has been assumed that the production and regulation of steroid hormones has been viewed as a multi-organ process involving glucocorticoids and sex steroids. However, active steroids can also be synthesized locally in target tissues, either from circulating inactive precursors or de novo from cholesterol. This may be the case in the brain for neurosteroids and in the immune system. Furthermore, recent evidence suggests that other steroid hormones LH, GnRH, ACTH and CRH are expressed locally in target tissues, potentially providing a mechanism for local regulation of neurosteroid and immunosteroid synthesis. The balance between systemic and local steroid signals depends critically on life history stage, species adaptations, and the costs of systemic signals. Thus, individual tissues and organs may become capable of autonomously synthesizing and modulating local steroid signals, perhaps interacting with the HPG and HPA axes and the overall response to stress (Schmidt et al., 2008).

5. Integration and regulation

The stress response is characterized by the interplaying of several centers, mechanisms and systems, in order to reestablish the homeostatic conditions. Although it has been known for long time that the stress response is initiated by the activation of the Sympathetic-Chromaffin (SC) and the hypothalamus-pituitary-interrenal (HPI) axes, it was also known from the beginning that other regulatory systems are involved from the initial stages in the building of the stress response. Thus, it was already described by Selye that some pathological components were usually included in the events related to the General Adaptation Syndrome, such as gastrointestinal ulcers and thymolymphatic atrophy, clear signs of immunosuppressed status. Later on, an increasing number of evidences obtained during the last decades, both in lower and higher vertebrates, indicate that the stress response includes also the immune system. Even at the early life stages, the neuroimmunoendocrine interaction is active under stress. Hence, an important number of interconnections are established after stress, not only between the nervous and the endocrine system, but also between the endocrine and immune system, thus constituting a complex network of transmitters between the three regulatory systems. Although this aspect has not been extensively studied in all vertebrates (Verburg-Van Kemenade et al., 2009), it seems apparent that in all of them the nervous, endocrine and immune systems do not operate independently but rather they are part of the repertoire of the physiological

responses available to react in front of particular circumstances out of the normal physiological range, i.e.: disease, exercise, extreme environmental changes. Communication between these three physiological systems has had less attention in lower vertebrates compared to mammals, mainly because the amount of effort dedicated to such species is less and because of the lack of specific biochemical tools. However, such functional connections are present in all vertebrates and therefore this interconnection network may be an early mechanism in the evolution (see figure 2).

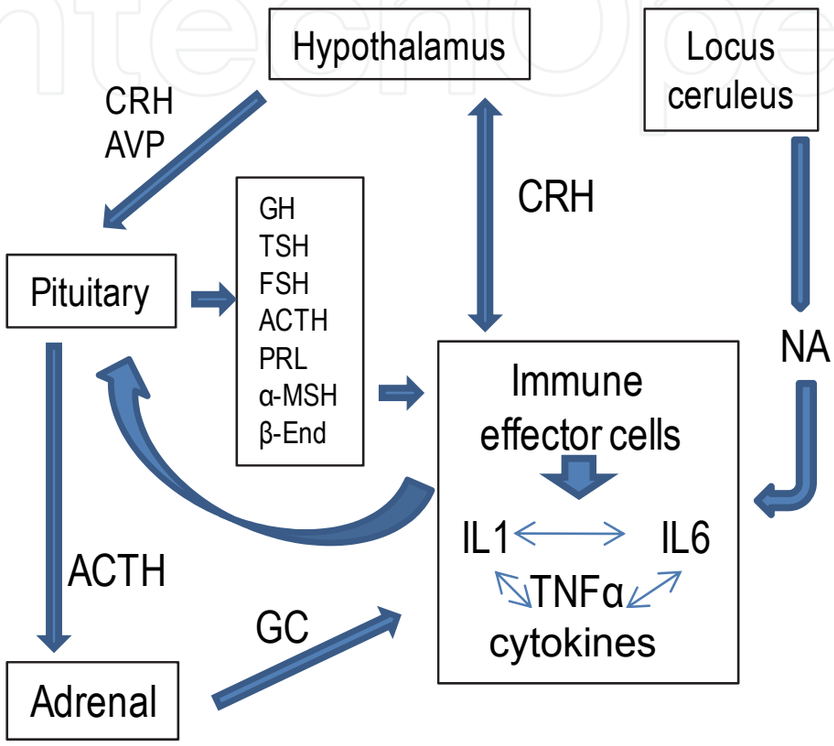

Fig. 2. Stress axis and main neuroimmunoendocrine interactions

These interactions start already at the central levels and there are multiple sites of interaction among the various components of the stress system. Neural control of stress is a complex process that requires the integration of information regarding both actual and potential outcomes. The organization of stress pathways further suggests that inputs on the physiological status of the animal can contribute to the eventual endocrine or autonomic response to the stressor. The majority of the pathways initiating physiological stress responses seem to be made at the level of limbic structures, which communicate information to subcortical sites positioned to interface with ongoing homeostatic feedback (Ulrich-Lai and Herman, 2009). The physical separation of autonomic and HPA stress effector circuits promotes some degree of independence of the two stress-modulatory cascades, allowing for appropriate tuning of neural and hormonal responses to specific demand characteristics of the actual or anticipated event. However, these two physiological systems also work together, both in terms of overlap in their underlying neural circuitry and in terms of their physiological functions. Charmandari et al., (2005) reviewed some of these connections. Reciprocal neural connections exist between the CRH and noradrenergic neurons of the

central stress system, with CRH and noradrenalin stimulating each other primarily through CRH type 1 and *a*1-noradrenergic receptors, respectively. Autoregulatory negative feedback loops are also present in both the PVN, CRH and brainstem noradrenergic neurons, with collateral fibers inhibiting CRH and catecholamine secretion via presynaptic CRH and *a*2-noradrenergic receptors, respectively. Both the CRH and the noradrenergic neurons also receive stimulatory innervations from the serotoninergic and cholinergic systems, and inhibitory input from the γ-aminobutyric acid (GABA)-benzodiazepine (BZD) and opioid peptide neuronal systems of the brain, as well as from the end-product of the HPA axis, the GCs (Charmandari et al., 2005). It is likely that dysfunctions of information processing across these circuits, resulting from environmental adversity and/or genetic factors, generate alterations that can culminate in maladaption.

In terms of the bidirectional relationships between endocrine and immune systems many of the hormones assessed so far can have an influence on immune agents or mechanisms, and even more some of them play significant roles in the regulation of the immune response. This is the case of the hypothalamic CRH and the adrenal hormone cortisol. The other axis related to stress, the sympathetico-chromaffin axis also influences immune response through catecholamines. In the reverse direction, the majority of evidence indicates that either direct or indirect stimulation of hypothalamic CRH secretion is the primary means by which cytokines (IL-1, IL-6, and TNF-α) activate the HPA axis. Thus, the neural pathways which IL-1 have been proposed to influence the neuroendocrine hypothalamus in mammals are numerous and diverse, including the inhibitory effects of either inhibitors of prostaglandin synthesis or disruption of catecholaminergic input into the hypothalamus (Turnbull and Rivier, 1999)

Moreover, a reduced number of family molecules appear consistently in the interconnection pathways in all vertebrates. For example, immunocytes can release Proopiomelanocortin (POMC)-derived peptides which have been shown to be involved in the regulation of the immune system. The Growth Hormone can stimulate the activity of the immune system. Sympathetic neurotransmitters can modulate the respiratory burst activity of trout phagocytes. Melanotropins, Melanocyte Stimulating Hormone (MSH), and Melanocyte Concentrating Hormone, (MCH) exert relevant stimulatory effects of the immune system. In mammalian species POMC is produced not only by neuroendocrine tissues, but also in lymphoid cells, which reinforces the neuroimmunoendocrine connection. More work has to be done to ascertain the regulatory mechanisms, and in particular, the role of the receptors and the role of putative paracrine mechanisms that may explain at some extent the interconnection mechanisms between regulatory systems.

This may be the case of organs such the head kidney in fish, as it concentrates several secretory cells belonging to either immune or endocrine systems. It should be emphasized that in fish the head kidney or pronephros is an important centre of the endocrine response. In fact this organ becomes key player in the organization of the integrated response to stressors. Head kidney plays a substantial endocrine role in the secretion of the two main hormones of the hormonal axes, cortisol from interrenal cells, the major fish glucocorticoid and mineralocorticoid, and catecholamines, released by chromaffin cells which are components of the sympathetic nervous system releasing, and receiving specific connections from the central nervous system [30]. Moreover, not only the neural and the endocrine system meet in this organ, but also the immune and hematopoietic systems are found in the pronephros. Thus, this organ is the homologous to the bone marrow of higher vertebrates which involves that the production of lymphocytes, monocytes and neutrophils is localized

in this organ. It is concluded, then, that the head kidney deals with a number of key physiological responses in fish species. Therefore, fish represent an interesting comparative model for the study of the stress effects on the nervous, endocrine and immune systems, due to the structure and composition of the head kidney (Tort, 2010). In summary, the concept of neuroimmunoendocrine connection identifying specific tissues with specific systems (lymphoid tissue/ immune system, gland/ hormones or neurones/ nervous system) appears to be no longer appropriate or complete as well in lower vertebrates [28]. Clearly in this case, the head kidney in fish represents a tissue in which all three regulatory systems are integrally connected forming a centralized network to coordinate endocrine, neural, and immune, responses after stress.

6. Stress and adaptation in vertebrates

The adaptive value of responsiveness to stressors in animals in nature may provide invaluable information regarding the dynamics and flexibility of neuroendocrine responses. Absolute levels of transmitters or hormones may not matter in the induction of responses and survival. Relative elevation or inhibition related to previous experience may adjust specific neural centers to produce relevant output specifically related to the appropriate environmental context. The neural mechanisms for transduction of relevant information are necessarily very plastic, with many transmitters, neuromodulators and peripheral hormone systems interacting between them. These systems influence behavioral and physiological stress responses, but are also influenced by that output (Greenberg and Summers, 2002).

Taking the whole amount of data on the research in stress, it can be said that it generally focuses on the use of negative stimuli. However, positive stimuli such as immediate reaction or novel rewards can cause comparable physiological stress responses (Ulrich-Lai and Herman, 2009). It has been proposed that acute rises in corticosteroids following perturbations of the environment may actually avoid chronic stress as they may work primarily as ''anti-stress'' hormones. Free-living populations may have elevated circulating levels of corticosteroids under emergency stages. However, this situation may not always be advantageous and there is accumulating evidence from birds that the adrenocortical responses to perturbating factors are modulated both on seasonal and individual bases. These data suggest that corticosteroid secretions allow flexibility so that the response is integrated in relation to time of year, time of the day, as well as for individual differences owing to body condition, disease and social status (Wingfield and Kitaysky 2002).

Although GC responses are viewed as a major evolutionary mechanism to maximize fitness through stress management, phenotypic variability exists within animal populations, and it remains unclear whether inter-individual differences in stress physiology can explain variance in unequivocal components of fitness. For instance, it has been shown that the magnitude of the adrenocortical response to a standardized perturbation during development is negatively related to survival and recruitment in a wild population of birds, providing empirical evidence for a link between stress response, not exposure to stressors, and fitness in a vertebrate under natural conditions. Recent studies suggest that variability in the adrenocortical response to stress may be maintained if high and low responders represent alternative coping strategies, with differential adaptive value depending on environmental conditions (Blas et al., 2007). In fish it has been shown that such a coping strategy is an important determinant of the physiological response, either in behavior, physiology and even gene expression, and therefore much of the phenotypic expression

may be significantly conditioned by the coping strategy, not only in one species but specifically in groups of individuals (Mackenzie et al., 2009).

7. Conclusion

All living organisms have developed responses to face stress situations, and some at cellular level such as heat shock protein activation, have been well conserved along evolution. In vertebrates the physiological stress response is driven by the neuroendocrine axes which in turn affect many other physiological compartments until the homeostasis is regained. In this chapter, after revisiting the stress concept, we have reviewed the general character of the stress phenomenon and the cellular responses, and afterwards we summarize the physiological stress response in vertebrates: mammals, birds, reptiles, amphibians and fish. Finally, the consequences of the endocrine activation and the neuroimmunoendocrine integrated response to stressors have been reviewed in relation to the adaptive value of the stress reaction.

8. Acknowledgements

The authors want to thank the support of the Spanish Ministry of Science and Innovation (BFU2009-07354) and Generalitat de Catalunya (SGR2009-0554). LT and MT are members of the Xarxa de Referencia en Aquicultura de Catalunya.

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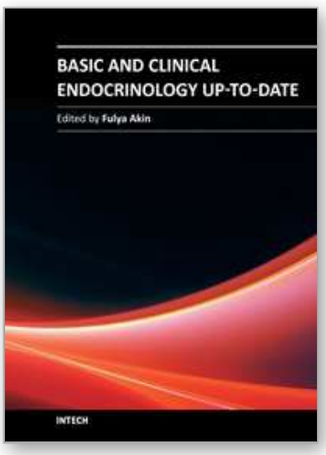

Basic and Clinical Endocrinology Up-to-Date

Edited by Dr. Fulya Akin

ISBN 978-953-307-340-8
Hard cover, 350 pages
Publisher InTech
Published online 17, October, 2011
Published in print edition October, 2011

This book provides the most up-to-date information on the basic and clinical aspects of endocrinology. It offers both researchers and clinicians experts, gold-standard analysis of endocrine research and translation into the treatment of diseases such as insulinoma, endocrine disease in pregnancy and steroid induced osteoporosis. Investigates both the endocrine functions of the kidneys and how the kidney acts as a target for hormones from other organ systems. Presents a uniquely comprehensive look at all aspects of endocrine changes in pregnancy and cardiovascular effects of androgens.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Lluis Tort and Mariana Teles (2011). The Endocrine Response to Stress - A Comparative View, Basic and Clinical Endocrinology Up-to-Date, Dr. Fulya Akin (Ed.), ISBN: 978-953-307-340-8, InTech, Available from: http://www.intechopen.com/books/basic-and-clinical-endocrinology-up-to-date/the-endocrine-response-to-stress-a-comparative-view

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