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Integrative Physiological Insights into Molecular Mechanisms of Stress Adaptation in Vertebrates (Article Review)

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Abstract

All vertebrates have evolved a highly sophisticated system of physiological and molecular responses to stress. Acute stress results in a fast neuroendocrine and autonomic activation, like HPA and SAM axes, cardiovascular changes, changes on respiratory function or metabolic alteration. Molecularly, stress activates heat shock proteins, mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt signalling pathways, antioxidant responses and transcriptional and epigenetic programming. In contrast, chronic stress results in maintained elevation of glucocorticoids that modulate immunity, plasticity of behavior and cognition, structural remodeling of the nervous system, or developmental or reproductive adaptation. These interlocking systems reveal the vertebrate ability to cope in the short term and adaptively alter plasticity in the long run, weighing survival against potential physiological costs. An understanding of these mechanisms is key to the interpretation of stress responses in ecological, clinical and experimental research.

Keywords: Stress adaptation, Vertebrates, Neuroendocrine response, Molecular mechanisms.

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1. Introduction

The concept of stress is central to vertebrate physiology, originally defined as any internal or external challenge that disturbed homeostasis and endangered organismal balance. Cannon's early work established the concept of "fight or flight" reactions that were mediated by afferent neural signals, while Selye subsequently extended this to include glucocorticoid-driven endocrine responses and set in place some of the cornerstones for modern stress physiology (1). Stress responses are crucial for survival, allowing organisms to sense and respond to environmental changes, metabolic perturbations, and life-history-related situations (2). Stress is also a physiologic incitement, when the nervous, endocrine and

immune responses are harmonized. The SAM axis mediates immediate effects by the rapid release of catecholamines, whereas long-term secretion patterns of glucocorticoids (cortisol in most vertebrates) are controlled by the HPA axis (2,3). These humoral signals coordinate multiple systemic effects, including cardiovascular responses, metabolism and behavior that enable the adaptation to a variety of stressors. Heat stress, for example, may affect the cellular functions such as membrane stability and gene transcription, and involve in endocrine regulation relying on activation of HPA axis, illustrating that adaptation to stresses is orchestrated at multiple tiers (4,5). Indeed, at molecular level adaptation response involves the induction of highly conserved stress protein or heat shock proteins (HSPs) that function as a class of molecular chaperone imperative for maintaining normal proteome under stressful environment (6). The increased expression of HSP70 and its homologues has been observed in a number of vertebrate taxa exposed to challenges other than thermal stress and this suggests that the contribution of this component in response to stress could be conserved (4, 7). In addition to stress proteins, signaling pathways (e.g., the PI3K/Akt pathway) and transcriptional networks are involved in determining cell survival abilities, antioxidant defenses and metabolic adaptations upon a targeted stressor (8). Comparisons show that the stress physiology is both conserved and species-specific among vertebrates. While the main architecture of stress signaling (https://en.wikipedia.org/wiki/Stress_(biology)#Molecular_aspects) pathways such as HPA-axis is to a large extent conserved across business (7, 8), their functional outputs and fine-tuning are rather different in various taxa, influenced by life histories, ecological environments and ongoing and past exposure to stress. That difference highlights the challenge of interpreting stress physiology as strictly based on shared vs. derived-derived adaptations. The molecular mechanisms of stress adaptations in the vertebrate have not only fundamental interest but also applied significance in zoo animal welfare, environmental biology and biomedicine (8, 9). Stress responses influence growth, reproduction and disease susceptibility in domesticated animals, partly through HSPs and acute-phase proteins that act as biomarkers for physiological stress (8,10). In the same way, studies of adaptation to stress in ecology highlight how animals respond to extremes and yet maintain physiological performance by coordinated molecular, cellular, and systemic mechanisms (10). This review aims to synthesize current integrative physiological and molecular insights into the mechanisms of stress adaptation in vertebrates, highlighting conserved pathways, regulatory networks, and key adaptive responses across taxa.

2. Stress Detection and Signaling Systems

Vertebrate stress sensing starts with nervous system perception of stimuli from internal and external sources, followed by transduction to activate coordinated endocrine actions. The hypothalamus is a pivotal integrator that receives incoming information from sensory pathways and drives neuroendocrine axes to combat threats. There are two major stress signaling axis in vertebrates: the sympathetic-adreno-medullary (SAM) axis and the hypothalamic-pituitary -adrenal (HPA) axis (11,12). The SAM axis is responsible for the immediate physiological response via release of catecholamines, including epinephrine and norepinephrine from chromaffin cells located in the adrenal medulla or their non-mammalian counterpart tissues (12). These catecholamines rapidly stimulate increased heart rate, breathing and mobilization of energy when the stressor is first detected in less than a few seconds to prepare the organism for action (“fight or flight”). This fast-responding activity of neurons is a characteristic of the first stage in the GSS (11). In contrast, the HPA axis mediates delayed but more enduring reaction. It is brought into action when corticotropin-releasing hormone (CRH) neurones in the paraventricular nucleus (PVN) of the hypothalamus secrete CRH into the portal blood system directed to the anterior pituitary. CRH counteracts with corticotroph receptors and activates the hypophysis to secrete Adrenocorticotrophic Hormone (ACTH), which, in turn, will stimulate the adrenal cortex to produce glucocorticoids like Cortisol or Corticosterone (13). These adrenal steroids are also released into the bloodstream and some of these effects in systemic metabolism, immune function, behavior allows organisms to adjust their responses at a sustained level beyond the initial threat (13,14). Glucocorticoids also function by negative feedback regulation, as they attach to glucocorticoid receptors in the hypothalamus and pituitary gland that suppress additional CRH and ACTH release and thereby diminish

overstimulation of the stress response (15). This feedback is important for homeostasis, ensuring that stress signaling is proportional to stimulus. In addition to these classic pathways, new findings point to stress signaling also cross-talking with other constructs uncovered in this study (i.e., cytokines in the immune system modulates HPA activity and amygdala mediates emotional processing of stress) (14). In addition, non-genomic glucocorticoid effects and rapid membrane signaling are also involved in the dynamics of stress detection and signaling, particularly during acute response (16).

3. Mechanisms of Stress Physiology in Vertebrates

Vertebrates react to stress through integrated adjustments in a variety of physiological systems, which are designed to maintain homeostasis and ultimately ensure survival. These responses are neural, endocrine, cardiovascular, respiratory and metabolic adaptations that come into play when an animal perceives a stressor (17,18), Table 1.

3.1. Cardiovascular Responses

Among the host of physiological effects in response to stress has emerged some of the most basic cardiovascular adjustments. Stimulation of the sympathetic nervous system raises heart rate and cardiac output in order to provide a rapid supply of oxygen and nutrients to tissues at times such as fight-or-flight situations. Stress also results in a blood flow redistribution that provides more of the circulatory volume to vital organs including the heart and brain. Chronic or recurrent stressors may also lead to poor functioning of the cardiovascular system, which indicates that long-term activation of stress responses can be maladaptive (19).

3.2. Respiratory Responses

Lung function is adaptively adjusted under stress to accommodate increased metabolic need. Ventilatory rate and depth also increased to a level that dyspnea-threshold cyclists would experience improvements in oxygen uptake and carbon dioxide output. It is reported stress modifies the physiological respiratory regulation and autonomic stress responses are correlated to modifications in breathing patterns (20). Such adjustments are essential when sudden demands such as exercise, hypoxia, or environmental extremes occur.

3.3. Endocrine and Metabolic Responses

Stress activates the hypothalamic-pituitary-adrenal (HPA) axis and stimulates release of glucocorticoids such as cortisol or corticosterone. These hormones are essential for regulating metabolism through stimulation of energy substrate mobilization, alteration in glucose production and alteration of immune function (21,22). Indeed, seasonal changes in production of glucocorticoids may occur in free-living vertebrates (e.g., refs 22), and hormone levels can change with life history stage due to the interplay between physiological condition and environmental needs.

3.4. Integration Across Systems

Physiological stress reactions are not confined to single systems, but represent a coordinated network of neural, endocrine and physiological actions. The interaction between the autonomic nervous system, HPA axis, cardiovascular and respiratory systems allows an integrated response to external and internal danger (17, 20).

Table 1: Physiological Responses to Stress in Vertebrates

Physiological System / Component	Role in Stress Adaptation	Reference
Cardiovascular adjustments	Increases heart rate and cardiac output to support rapid oxygen delivery and energy distribution during stress	19
Respiratory enhancement	Elevates ventilation rate and lung function to meet increased oxygen demand and eliminate	20

	CO_2	
Endocrine-mediated metabolic shifts	Glucocorticoids (e.g., cortisol) mobilize energy stores, regulate metabolism, and modulate immune activity	21,22
Neuroendocrine integration	Coordination between nervous signals and hormone release (via HPA axis) to support systemic adaptation	17,18
Homeostatic regulation	Interconnected responses across organ systems to maintain internal balance under stress	17,20

4. Molecular Mechanisms of Stress in Vetebratetes

The molecular mechanisms of stress adaptation include a variety of cellular processes that sense stressful stimuli, mount protective responses and ultimately alter organismal physiology in many tissues. Vertebrates use evolutionarily conserved mechanisms to sense and transmit stress signals, phosphorylating factors that act as effectors which induce a variety of cell-autonomous (adaptive) responses that help maintain cellular homeostasis and organismal integrity under a range of environmental challenges.

4.1. Heat Shock Proteins and Chaperoning Systems

Among the most highly conserved molecules associated with a response to stress is the family of heat shock proteins (HSPs). They are a family of molecular chaperones that supports unfolded or damaged polypeptides and help them to undergo correct refolding, respectively degradation. HSP expression, in particular the HSP70 and HSP90 families, is rapidly upregulated by stress situations like heat, hypoxia or toxic exposure leading to even higher capacity of cells/synapses to cope with proteotoxic stress (23). In fish, amphibians, birds and mammal's high concentration of HSPs is associated with increased resistance to heat stress and other forms of physiological stresses.

4.2. Stress Signaling Pathways

Response to cellular stress The signals mediating the response of a cell to stressful conditions, involve multiple intracellular pathways which couple external and internal signals:

- MAPK Pathways (Mitogen-Activated Protein Kinases): MAPK cascades including p38, JNK, and ERK modules are activated by stress. These kinases relay the stress signals to specific transcription factors, which trigger gene expression programs that regulate cell adaptation, modify inflammation and control apoptosis (24).
- PI3K/Akt Signaling: The phosphoinositide 3-kinase (PI3K)/Akt signaling cascade has been reported to be associated with cell survival and metabolic control in response to stress. Akt is known to suppress pro-apoptotic proteins and augment antioxidant defense, contributing to cellular resistance (25).

4.3. Oxidative Stress Modulation

Reactive oxygen species (ROS) are produced more copiously in periods of physiological stress, then when the exercise is prolonged, or temperature extreme and the metabolic status varies. Cells use antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathion peroxidase to reduce ROS damage (26). Increased expression of antioxidant genes is a common finding among vertebrates in relation to exposure to chronic or acute stress conditions, tying oxidative status with general response to stress.

4.4. Transcriptional Regulation and Epigenetic Control

Expression of stress exposure occurs at the level of transcription as well as on an epigenetic scale. Transcription factors, including NF-κB, AP-1 and HSF1 govern networks of stress-response genes. In

vertebrate's epigenetic modification including DNA methylation and histone acetylation might be involved in very long-term stress memory, phynotypic plasticity and increased future response to later soma millennia stress acti (27).

5. Adaptive Stress Responses in Vertebrates

Chronic stress in vertebrates describes repeated or sustained experience of stressors beyond an acute event. In contrast to short-term stress, which activates an immediate neuroendocrine and autonomic response, chronic stress causes prolonged activation of signaling pathways and hormones, resulting in enduring physiological adaptations that may be either beneficial or detrimental depending on the duration and context.

5.1. Neuroendocrine Adaptation

HPA axis activation is preserved during chronic stress, which results in prolonged exposure to elevated glucocorticoids (GCs) (cortisol or corticosterone). Early and repeated glucocorticoid exposure lead to changes in feedback sensitivity, receptor expression and gene regulation at the downstream level. These adaptations reset the stress signaling to a state that is appropriate enough for continuous stress exposure (28,29).

5.2. Immune Modulation

Extended stress has a two-sided influence on the immune system. Glucocorticoids initially inhibit immunity, but chronic treatment may result in immune dysregulation, with occasional low-grade inflammation. This is common in vertebrates across species, influencing susceptibility to infection (30), autoimmunity risk (31) and wound healing.

5.3. Metabolic Adjustments

Metabolism is altered by chronic stress in order to support energy supply. Increased glucocorticoids promote gluconeogenesis, lipolysis, and protein catabolism, frequently at the cost of growth and reproduction. Energy partitioning favours survival more than the long term aspects of physiology (32,33).

5.4. Behavioral and Cognitive Plasticity

Behaviour and cognition are affected by chronic stress. Chronic activation of HPA and SAM axes leads to anxiety-like behavior, disrupted feeding, or cognitive deficits. These adjustments can be construed as maximizing survival in a pernicious long-term threat laden ecology, characterized by adaptive behavioral plasticity (34,35).

5.5. Neural Remodeling and Structural Plasticity

The hippocampus, amygdala, and prefrontal cortex undergo structural remodeling with chronic stress. Dendritic reorganization, synaptic redistribution and neurogenesis contribute to adaptive effects in the long-term, but may also set the stage of maladaptive states when mechanisms for compensation are not successful (36,37).

5.6. Reproductive and Developmental Effects

Reproductive hormones (GnRH, LH, FSH) are altered by chronic stress and may inhibit reproduction. In development, stress could change growth trajectory, organ maturation and genetic modifications through epigenetic mechanisms with transgenerational effects in some cases. Collectively, these mechanisms demonstrate that vertebrates modify at multiple levels of organization to chronic stress in order to survive while minimizing potential long-term costs (38).

6. Conclusions

Stress in vertebrates is a complex multi-level system of molecular, cellular, physiological and behavioural adjustments. Whereas acute stress enables immediate survival by evoking rapid

neuroendocrine activation, cardiovascular and respiratory adjustments, and metabolic mobilization, chronic stress episode calls for a wider palette of longer-term responses including glucocorticoid-mediated immune modulation, neural remodeling or behavioral plasticity and even developmental or reproductive modifications. Taken together, these responses demonstrate how vertebrates are able to both cope acutely and adapt plastically over life history for coping chronically, thereby maintaining homeostasis in a wide range of internal and environmental conditions. Bringing these integrated phenomena into focus offers key insights to understanding the physiological thresholds, resiliency and potential trade-offs linked with sustained exposure to stress in vertebrate taxa.

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