International Journal of Veterinary and Animal Medicine

ISSN 2517-7362

Heat Stress and Livestock Adaptation: Neuro-endocrine Regulation

A.Afsal[1, 2]
V.Sejian[2*]
M. Bagath[2]
G.Krishnan[2]
C. Devaraj[2]
R.Bhatta[2]

[1]Academy of Climate Change Education and Research, Kerala Agricultural University, Vellanikkara, Thrissur, Kerala, India

[2]ICAR-National Institute of Animal Nutrition and Physiology, Adugodi, Bangalore-560030, India

Abstract

Heat stress is the major intriguing factor influencing livestock production in the changing climatic condition. Therefore, research efforts are needed to identify thermo-tolerant breeds which can help to optimize livestock production during heat stress challenges. The heat tolerance in livestock is determined through various mechanisms and neuroendocrine regulation is one of the crucial pathways by which the animal survives the stressful condition. Hence, this paper is an attempt to elucidate the hidden intricacies of neuroendocrine mechanisms which helps the livestock to survive in a specific environment. The hypothalamic-pituitary-adrenal (HPA) axis plays a significant role in the release of several neurotransmitters and hormones which regulates the thermoregulatory mechanisms in animals. The corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids are the primary products of HPA axis which ultimately controls the stress response pathways in animals. The HPA axis regulates the energy partitioning for supporting the life-sustaining activities through the process of hepatic gluconeogenesis. Epinephrine and norepinephrine levels are found to be increased in heat stressed animal. These neurotransmitters regulate the cardiovascular rate during heat stress and ensure supply of blood to vital organs. The thyrotropin-releasing hormone (TRH), thyroid stimulating hormone (TSH) and thyroid hormones (T3 and T4) are the components of metabolic pathway in regulating body heat production. Further, leptin secreted from adipocytes also considered being negatively influencing stress response. Further, aldosterone plays a pivotal role in electrolyte and fluid homeostasis and regulation of Na + and K+. The lactogenic hormone prolactin was found to be decreased while somatotropin hormone level was increased during heat stress reflecting negativity in milk production and growth. This indicates the complexity of the interaction between the neuro-endocrine regulators to maintain homeostasis during heat stress in livestock. Generally, cortisol and thyroid hormones are considered to be important biological markers of neuro-endocrine pathway regulation of adaptive mechanisms during heat stress in livestock.

Keywords

Climate Change; Heat stress; Adaptation; Neuro-endocrine pathway; Production

Introduction

Climate change has emerged as the major threat to the world economy. It has turned up to be the global phenomenon threatening the survival of many ecosystems worldwide. The increased concentration of greenhouse gases (GHGs) in the atmosphere causes the greenhouse effect, resulting in climate change. Heat waves will occur more habitually and last longer that leads to extreme precipitation and fluctuating weather conditions in many regions of the world [1]. Sea level is projected to increase 0.45 to 0.82m by the end of 2100 which has deleterious effects on both natural and human ecosystem [1].

Increased frequency of life-threatening events like cyclones, droughts, floods, tsunami, and wildfires are expected to happen in the changing climate scenario. Among the agricultural sector, crops and livestock are particularly vulnerable to the devastating effects of climate change ultimately deteriorating the agricultural production [2].

Heat stress emerges as one of the primary direct impacts of climate change which drastically affect the agriculture production. The severity of heat stress can be assessed by THI index (temperature-humidity index), which is one of the well-established tools to analyze the thermal stress worldwide. However, the effects of heat stress are further influenced by relative humidity, solar radiation, and wind speed. But the THI only takes into account the temperature and humidity effects without considering wind speed and solar radiation. This warrants further investigations to identify a more appropriate index to quantify the impact of climate change [3].

All animals have a defined thermoneutral zone, wherein they maintain the normal

Article Information

DOI: 10.31021/ijvam.20181108
Article Type: Review Article
Journal Type: Open Access
Volume: 1 **Issue:** 2
Manuscript ID: IJVAM-1-108
Publisher: Boffin Access Limited

Received Date: May 08, 2018
Accepted Date: May 24, 2018
Published Date: May 28, 2018

*Corresponding author:

Sejian V
Senior Scientist
Animal Physiology Division
National Institute of Animal Nutrition and Physiology
Adugodi, Bangalore-560030
India
Tel: +91-9740726121
Fax: +91-080-25711420
E-mail: drsejian@gmail.com

Citation: Afsal A, Sejian V, Bagath M, Krishnan G, Devaraj C, Bhatta R. Heat Stress and Livestock Adaptation: Neuro-endocrine Regulation. Int J Vet Anim Med. 2018 May;1(2):108

body temperature without altering its behavioral and physiological functions. Any deviations in this zone may ultimately end up in altering the normal physiological mechanisms to cope with the adverse environmental temperature [4]. Thermal stress may affect the productive functions such as milk, meat and reproductive performance [5]. Behaviorally in order to cope up to the heat stress challenges, animals generally increase their water intake and reduce their feed consumption. Thermoregulatory mechanisms to heat stress are species specific and therefore, the magnitude of reduction in their production performance also differs between them.

Endocrine responses are one of the principal regulators of animal adaptation to heat stress challenges. The hypothalamo-pituitary adrenal (HPA) axis play an integral role in regulating the neuro-endocrine mechanism during heat stress condition [6]. This review is an attempt to gather information pertaining to neuro-endocrine mechanisms which help the livestock to survive in a specific environment. Apart from addressing in detail the neuro-endocrine mechanisms of livestock adaptation to heat stress, the review also attempts to elucidate the mechanisms by which the production pathways are compromised in an effort to supply energy resources for maintaining the vital functions of the body.

Climate Change and Heat Stress

Climate change is the most critical global issue that hampers both human welfare as well as the global ecological balance. Rising fossil fuel burning and land use changes have emanated, and are emitting a large number of greenhouse gases into the earth's atmosphere. This increases the global temperature ultimately resulting in climate change. The most concerned global consequences of climate change include the elevating sea surface temperature and rising sea level accompanied by the melting of glaciers and ice caps in a polar region. According to IPCC, average global earth surface temperature change for the first three months of 2016 was 1.48°C. Predicted range of increase of the earth surface temperature by the end of 2100 is 1.4 to 4.8°C according to the climate model projection outcome [1].

Another global concern faced today is the expanding human population. Projection is that by 2050 human population would surpass 9.6 billion which would create a global crisis especially from the food security perspective [2]. In fact, food security is one of the large sectors which is detrimentally affected by the changing climate scenario because of the disquieting consequences of the agriculture production [2]. Over-exploitation of resources by human also adversely affects the global ecological balance, thereby contributing to climate change. The vagaries of climate change have emerged as the major threat to the present as well as future capacity to produce food, feed, fiber, and fuel for the growing population [7].

Heat stress is one of the major intriguing factors associated with the changing climatic condition. Global temperature is rising at an alarming level. All biotic organisms possess a thermo neutral zone within which their biological functioning will be optimum [8]. The rise in ambient temperature negatively affects the productive functions in all organisms. The internal mechanisms of plants, animals, and intrusive alien species get altered as a result of a change in environmental conditions thereby altering the sustainable production of these species. As an ultimate consequence, agriculture and livestock sector which are the major contributors in securing food security get destabilized by climate change.

Heat Stress Impact on Livestock Production

Heat stress has emerged as one of the major concern to the farmers which hamper the livestock production in a drastic manner. Also, climate and geographical pattern are the most significant factors which emerged to be a major concern among poor and marginal farmers. In addition to that climatic parameter such as ambient temperature and rainfall pattern are also influenced in the pasture and forage production [9]. The impact of heat stress might reduce the feed intake and increase the water consumption in animals, and in extreme conditions causes death [9]. The effects of heat stress are evident in feed consumption, production efficiency in terms of milk yield or weight gain per unit of feed energy, growth rate, egg production, and reproductive efficiency [10]. Moreover, heat stress would affect the livestock production in a drastic manner by altering the supply of essential nutrients through feed availability. The animal reduces its feed intake for reducing the energy metabolism by as a part of the behavioral response of the animal [3]. Further, the respiration rate of the animal was increased during the heat stress which ultimately causes respiratory alkalosis and acid-base imbalance. Moreover, the animal compromises its productive functions by deviating most of their energy expenditure to coping harsh climatic conditions [11].

Significance of Livestock Adaptation

Adaptation is the morphological, anatomical, physiological, biochemical and behavioral characteristics of the animal which promote the welfare and favors the survival of the animal in a specific environment. Heat stress can cause a significant effect on livestock production mainly by decreasing the feed and water availability [4]. Therefore, sustainable production from livestock requires well adaptation of the animals to the testing climatic conditions [12].

The animals' exhibit various adaptive responses like increased respiration rate, panting, sweating and decreased metabolic activity [13]. Utilization of energy for the adaptive mechanisms will reduce the productive and reproductive performances [12]. The well-adapted animals require less amount of energy to cope up with extreme conditions. In addition, increased feed conversion rate is also expressed in well-adapted animals than the less adapted ones [9].

Climate change is a major threat to the livestock sector. Hence effective implementation of climate resilient adaptation pathways will move towards the sustainable livestock development.

Different Mechanisms of Livestock Adaptation to Heat Stress

The biological response to stress is divided into acute and chronic phases, with the acute phase lasting hours to a few days and the chronic phase lasting several days to weeks [14]. However, it might depend on the severity of stress which hampers the animal production and the survivability of the animal in extreme climatic conditions. In order to maintain the homeostasis, the animal has to control their thermoregulatory mechanism by implementing certain adaptive responses. There are various adaptive responses exhibited by the animal when exposed to different environmental stresses, such as behavioral, physiological, blood biochemical, cellular and neuro-endocrine responses. However, the most significant behavioral changes observed mainly during heat stress conditions are seeking shade, increased standing time, reduced feed intake and more consumption of water [15]. Further, increased respiration rate, sweating rate, and rectum temperature illustrate the effect of physiological adaptive responses [16]. In addition, Taylor et al. [17] reported that body temperature is also considered as ideal indicators to reflect the impact of a range of stresses in animals and it represents the whole thermoregulatory mechanisms in the animal body. Moreover, physiological responses are one of the primary pathways by which the animal survive in extreme environmental conditions.

Blood biochemical responses shown by the animal might have influenced by certain factors like nutrition, sex, age, diseases and stress factors. Heat stress significantly alters the levels of hemoglobin (Hb), packed cell volume (PCV), plasma and glucose level in the blood. Also, Etim et al. [18] denoted that both Hb and PCV increased significantly in goats during exposure to severe thermal stress. Further, the effect of heat stress increases the level of oxygen consumption of the animals by influencing the respiration rate [19]. Moreover, the increased levels of oxygen consumption reduce the partial pressure of carbon dioxide in the blood and ultimately result in respiratory alkalosis [3]. The increased PCV during heat stress condition could be attributed to severe dehydration of these animals [20].

Cellular response is one of the genetic adaptive mechanisms shown by the animal to overcome the severity of heat stress [21]. Gene expression changes include various molecular mechanisms pertaining to the different type of cells. This indicates that various

tissues respond to the temperature above the thermo-neutral zone by bringing in the cellular adaptive responses which determine the genetic characteristics which ultimately controls the cellular homeostasis [22]. Typically, the thermo tolerant genes like heat shock proteins (HSP) and slick hair gene expression indicate the severity of heat stress in farm animals [23]. They are activated by heat shock factors (HSFs) and their expression increased when cells are exposed to extreme heat stress. Heat stress-induced secretion of HSFs also stimulates both the endocrine and immune system via extracellular secretion of HSP. The various cellular responses to heat stress include: inhibition of DNA synthesis, transcription, RNA processing, translation, the progression of cell cycle, disruption of cytoskeletal elements, protein denaturation and changes in membrane permeability. It is a well-established fact that the changes in gene expression are an integral part of the cellular response to heat stress [24]. The HSP70 concentration in blood was also identified as a reliable indicator of chronic stress in feedlot cattle [25]. Apart from cattle, HSP70 was also identified to be a confirmatory molecular marker to quantify heat stress response in different farm animals [26].

Stress is an external event or condition that places a strain on a natural system. During stress, various endocrine responses are involved in improving the surviving ability of the animals. The Hypothalamus-Pituitary-Adrenal (HPA) axis is primarily responsible for the adaptive component of the neuro-endocrine stress response. Endocrine responses are one of the principal regulators of animal adaptation during exposure to challenging environments. Further, the extreme level of stress may result in inducing changes in the secretion of all hypothalamic and pituitary hormones which alters the metabolism, immune response and behavior apart from altering the reproductive performance. The principal hormones which govern the animal adaptation include glucocorticoids thyroid hormones, catecholamines, antidiuretic hormone and growth hormone. When the animal is exposed to extreme environmental stress it results in the activation of the hypothalamo-pituitary adrenal axis (HPA) and sympatho-adrenal medullary axis (SAM). Generally, neuro-endocrine regulation was considered to be the principal regulator of all adaptive mechanisms which helps the animals to survive the stress. Figure 1 deciphers the various neuro-endocrine mechanisms exhibited by farm animals to survive the stressful condition.

Neuro-endocrine Mechanism of Adaptation in Livestock

Stress responses promote the maintenance of homeostasis and adaptation to the various physiological and psychological challenges pertaining to the changes in the environment. This complex process involves coordinated activation of behavioral, physiological and particularly neuroendocrine regulation in the animal. Functional properties of the stress response systems show large interindividual variation, depending upon a variety of factors including genetic predisposition [27]. Moreover, the relative effect was mainly dependent upon the duration and intensity of the various stressors associated with livestock production.

Neuro-endocrine regulation is one of the principal adaptive responses shown by the animal in extreme stress condition [28]. Hypothalamo-pituitary-adrenal (HPA) axis plays a significant role in the release of several neurotransmitters and hormones which regulates the thermoregulatory mechanisms in animals. The HPA axis gets activated when an animal receives stress through various sense organs and also the response to the stimulus is coordinated by brain center. Further, it might activate the adaptive responses pertaining to the neuro-endocrine system of the animals. The activation of the HPA axis may be related directly or indirectly to factors such as heat stress, drought and nutritional stress and also due to disease occurrence. The corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids are the primary products of HPA axis which ultimately controls the stress response pathways in animals [29]. Moreover, ACTH is the important regulator which helps in the production and secretion of cortisol [4]. Also, several research findings showed that the hormones produced by the adrenal and thyroid glands recognized to have a significant role in thermoregulation and metabolic response in livestock animals [15, 11]. Further, the activation of HPA axis may result in enhanced production glucocorticoids like cortisol, which is indicated as the major stress-relieving hormone and also identified as a reliable biomarker for assessing the severity of stress cutting across species [15]. Also increased level of cortisol would favor hepatic gluconeogenesis which helps in the production of glucose from

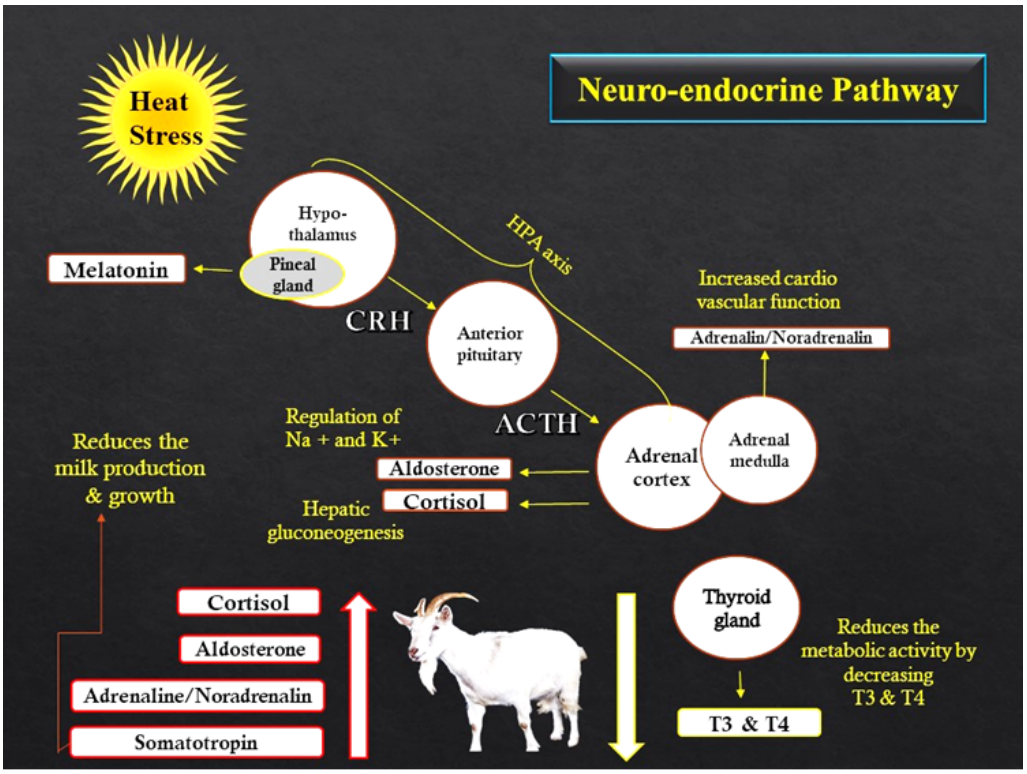

Figure 1: Neuro- endocrine adaptive mechanism in farm animals during heat stress conditions

non-carbohydrate sources and maintains the energy metabolism to support life-sustaining activities. Several authors denoted that the secretion of glucocorticoids is the principal endocrine response to heat stress condition [11,26]. Glucocorticoids have been widely used in experimental research in farm animals and also used as a useful variable for analyzing the animal welfare. Moreover, their stimulation may be influenced by a wide variety of factors with respect to the individual animal and sex, age, and physiological stage [30]. Interestingly, parturition in some species was regulated by the activation of the HPA axis [31]. Application of non-invasive techniques for monitoring glucocorticoid metabolites in fecal samples is a useful tool for assessing the animal welfare of various farm animals. Another important endocrine product secreted from adrenal gland is the aldosterone which involves in the regulation of electrolyte mechanism in the animal. Further, the aldosterone level was reported to be higher in the heat-stressed animal rather than the controlled group animals after providing them with adlibitum feed and water [32]. Moreover, the animals during heat stress conditions are subjected to severe dehydration which might result in the activation of the renin-angiotensin-aldosterone pathway to restore the fluid and electrolyte balance [3]. Likewise, the pineal gland is a neuro endocrine transducer, which is responsible for the melatonin production and influences the seasonal changes pertaining to the reproductive capability in different animals [33]. There are scientific reports available to illustrate the significant increase of melatonin level during heat stress and it clearly indicates the anti stressogenic effect in the animals [4]. Finally, the significant effect of glucocorticoid on melatonin level during heat stress establishes adrenal-pineal gland relationship which was evident in the importance of menacing the animal productivity mainly in tropical countries. Understanding the characteristics of melatonin would assist in implementing a new methodology for the photoperiod-dependent breeding programme in animals by inducing changes in the perception of photoperiod and the annual pattern of reproduction [34]. Similarly, the thyroid gland produces two types of hormones triiodothyronine (T3) and thyroxine (T4) which aid the regulation of metabolic activity in the animal. The decline in the level of metabolic hormones is to reduce the metabolic heat production during heat stress condition in goats [29]. Also, the author denoted that the functions of thyroid glands are mainly dependent on the environmental condition the animals are exposed to. Aleena et al. [11] reported that the changes in the ambient temperature suppresses the activity of thyroid hormone in blood level and also identified these hormones to be the stress indicators for assessing the heat tolerance in the farm animals. Generally, lower activity of the thyroid gland s helps to reduce the metabolic energy expenditure of animals coping them to extreme environmental conditions. Similar results of inhibited thyroid hormone concentration level were also reported in various livestock species like cattle, sheep and goats were exposed to thermal stress [4,15]. This could be an adaptive response shown by the animals to regulate the internal metabolic heat production without compromising the vital functions of the body [23]. Further, the lower levels of the thyroid hormones could be partially attributed to the compromised nutritional status of the heat-stressed animal, which could be attributed to the lower feed intake associated with behavioral adaptive responses [35]. There are research findings showing the reproductive capability of the animals also are compromised during extreme stress condition and alter the concentration and mechanism of different types of hormones associated with reproductive functions [36]. Further, the plasma estradiol level decreased drastically while the progesterone concentration increased during heat stress condition [4].

The interleukin-1, interleukin-6, and tumor necrosis factor are associated with the stimulation of stress axis. Cytokines are also stimulating the secretion of the hormone leptin from adipocytes. Significant reduction in the leptin concentration during heat stress condition in several farm animals has also been reported. This was attributed to the drastic reduction in the feed intake and the conversion of all non-carbon sources into glucose as a part of both behavioral and Neuro-endocrine responses [37]. Leptin is now recognized as an inhibitor of stress axis activity [38]. Therefore, both leptin and glucocorticoids complete the negative feedback circuit to suppress stress axis activity to maintain the homeostasis. Future studies are required though to establish the relationship between hormonal mediators, immune cytokines, brain neurochemicals, and stress axis activation for identifying other important traits associated with neuro-endocrine regulation of heat stress in farm animals. The importance of the hypothalamic–pituitary–adrenal (HPA) axis and glucocorticoids in modifying the inflammatory and cytokine response is highlighted in various studies in adrenalectomized animals. Likewise, most of the comparative studies shown the significant variation of endocrine responses in farm animals and these findings strongly established breed differences in the behavior of HPA axis during extreme environmental condition [34]. These efforts might help in developing new heat-tolerant breeds, which can survive and produce optimally in harsh environmental conditions.

The HPA axis

Hypophysiotropic neurons localized in the paraventricular nucleus (PVN) of hypothalamus synthesize and secrete corticotropin-releasing factor (CRF). The CRF was recognized as the principal regulator of the HPA axis. In response to stress, CRF is released into hypophysial portal vessels that influence the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) [39]. The binding of CRF to its receptor on pituitary corticotropes stimulate the release of ACTH into the systemic circulation [40]. Also, the principal target for circulating ACTH is the adrenal cortex, where it stimulates glucocorticoid synthesis and secretion from the zona fasciculata. Glucocorticoids are the downstream effectors of the HPA axis and regulate the physiological process by inducing changes in the intracellular receptors [41]. The biological effects of glucocorticoids help the animal in coping with extreme stress conditions. However, the extent of synthesis and stimulation of glucocorticoids influence the functioning of HPA axis and might affect the health of the animal [42].

CRF receptors

The physiological actions of the CRF family of peptides are mediated through two different receptor subtypes belongs to the class B family of G-protein coupled receptors [43]. The CRFR1 is expressed at high levels in the brain and pituitary and low levels in other peripheral tissues [12]. The highest levels of CRFR1 expression are found in the anterior pituitary, olfactory bulb, cerebral cortex, hippocampus, and cerebellum [44]. The CRF1 is activated through the binding of CRF-agonist and the ligand binding and subsequent receptor conformational change depend on three different sites in the second and third extracellular areas of CRF1. Considering the major tissues, CRF1 is coupled to a stimulatory G-protein further stimulate the adenylyl pathway, and ligand-binding triggers an overshoot in the cyclic adenosine monophosphate level which acts as a secondary messenger for numerous biological process [44]. However, the signal can be transmitted along multiple signal transduction pathways, depending on the structure of the receptor and the region of its expression. Alternate signaling pathways are stimulated by CRF1 which includes the activation of protein kinase c and mitogen-activated protein kinase [45]. CRF1 was also identified as a potent mediator of endocrine, autonomic, behavioral and immune responses to chronic stress conditions [46].

Vasopressin

Vasopressin (AVP) is a non-peptide that is highly expressed in the PVN, supraoptic (SON), and suprachiasmatic nuclei of the hypothalamus. Further, magnocellular neurons of the PVN and SON act together to stimulate the posterior lobe of the pituitary and release AVP directly into the systemic circulation for retaining the osmotic homeostasis [47]. In addition to magnocellular neurons, parvocellular neurons of the PVN synthesize and release AVP into the portal circulation, where this peptide potentiates the effects of CRF on ACTH release from the anterior pituitary.

The synergistic effects of AVP on ACTH release are mediated through the vasopressin V3 receptor on pituitary corticotropes. Further, binding of AVP to the V3 receptor activates phospholipase C by coupling to Gq proteins. Further, activation of the phospholipase

C stimulates protein kinase C, resulting in the potentiation of ACTH release [47]. Several investigators have reported that the expression of AVP in parvocellular neurons of the PVN and V receptor density in pituitary corticotropes is significantly increased in response to chronic stress [48]. Furthermore, it is already identified that AVP plays an important role in the stress response by maintaining the level of ACTH during chronic heat stress condition.

Adrenocorticotropic Hormone

When the animal is subjected to heat stress, multiple alterations takes place in the endocrine system such as the HPA axis. Among them, the main feature of the stress reaction is the activation of the HPA axis leading to the increase of ACTH [44]. ACTH is one of the important pituitary hormones which helps in supporting the growth and development of adrenal cortex and stimulating the synthesis and secretion of glucocorticoids. Therefore, the secretion of glucocorticoids depends on the integrity of the HPA axis and further the anterior pituitary secretes ACTH and the adrenal cortex synthesis Cortisol for regulating the behavior and neuroendocrine activities associated with the heat stress [15,46]. Therefore, ACTH and cortisol are often considered as the most important indicator for assessing the quantum of stress.

Proopiomelanocortin (POMC) is a prohormone that is highly expressed in the pituitary and the hypothalamus. POMC is processed into a number of bioactive peptides including ACTH, β-endorphin, β-lipotropic hormone and the melanocortins [43]. In response to CRF, ACTH is released from pituitary corticotropes into the systemic circulation where it binds to its specific receptor in the adrenal cortex. ACTH binds to the melanocortin type 2 receptor (MC2-R) in parenchymal cells of the adrenocortical zona fasciculata. Activation of the MC2-R induces stimulation of cAMP pathway events that induce steroidogenesis and the secretion of glucocorticoids, mineralocorticoids and androgenic steroids [46]. Specifically, ACTH promotes the conversion of cholesterol into 5-5 pregnenolone during the initial step of glucocorticoid biosynthesis.

Glucocorticoids

Glucocorticoids are transported through the circulatory system with the help of carrier proteins. The carrier proteins influence the glucocorticoids to be available rapidly after initiation of the stress responses [49]. Among the various glucocorticoids produced, cortisol is the principal hormone which controls the stress response in large ruminants in particular. Albumin is the major carrier protein for cortisol, although cortisol could be transported by cortisol binding globulin called transcortin. Approximately 1–10% of cortisol circulates as a “free” steroid through the circulatory system. In addition to that, the different types of tissue have the ability to regulate the available cortisol in a proper manner with the help of 11β hydroxysteroid dehydrogenase enzymes which converts cortisone to cortisol during stress.

Glucocorticoids have regulatory actions and mainly help to moderate the mobilization of energy expenditure throughout the body with the objective to retain the homeostasis [10]. Furthermore, glucocorticoids can affect the concentration of non-esterified fatty acids, lactate, plasma insulin and although having a variable effect on glucose metabolism [10,33,37]. In addition to that, cortisol converts all non-carbohydrate sources into glucose through the process of hepatic gluconeogenesis for supporting the energy requirements of vital organs. Glucocorticoid secretion was found to be highly variable in many species including cattle and sheep during stress [50]. Also, glucocorticoids are synthesized in a diurnal pattern that is governed by many factors including genetics [50].

Negative feedback Mechanisms associated with Glucocorticoids

Glucocorticoids modulate the HPA axis through the negative feedback mechanisms. Glucocorticoids have the capability to inhibit the activation of HPA axis through a delayed feedback mechanism and this control was determined by the circulating glucocorticoid concentration [30]. The delayed feedback system acts through transcriptional alterations and is regulated by GR localized in the brain region. Following binding of glucocorticoids, GRs modulate transcription of HPA components by binding to GREs or through interactions with transcription factors [49]. Glucocorticoids have a low nanomolar affinity for the GR and extensively occupy GRs during periods of elevated glucocorticoid secretion that occur the following stress. Mineralocorticoid receptors (MRs) have a sub nanomolar affinity for glucocorticoids, a restricted expression pattern in the brain and bind glucocorticoids during periods of basal secretion [73]. Also, the distinctive function of these two receptors suggests that MRs regulate the basal HPA tone while GRs mediate the glucocorticoid negative feedback mechanisms [51].

GRs are widely expressed in the brain, and thus the precise anatomical locus of glucocorticoid negative feedback remains poorly defined. However, two regions of the brain appear to be key sites for glucocorticoid feedback inhibition of the HPA axis. High levels of GR are expressed in hypophysiotropic neurons of the PVN, and local administration of glucocorticoids reduce PVN neuronal activity and attenuate adrenalectomy-induced ACTH hypersecretion. Several research findings suggest that the PVN is an important site for glucocorticoid feedback inhibition of the HPA axis [52]. The hippocampus has been implicated as a secondary site for glucocorticoid negative feedback regulation of the HPA axis [53]. The hippocampus contains a high concentration of both GR and MR and infusion of glucocorticoids into this structure reduces basal and stress-induced glucocorticoid release [51,54].

Role of HPA axis in Neuro-endocrine Regulation

The biological functioning and regulation of HPA axis is the primary requirement of adaptive mechanisms in the farm animals. The HPA axis is activated in response to the different environmental stressor, particularly heat stress in order to help the animal to cope with extreme environmental conditions [55]. Cortisol is recognized to be the stress relieving hormone and synthesized as the main product of the activation of the HPA axis and evokes a response from specific target receptors, eventually retaining homeostasis back to normal stage [56]. However, prolonged stimulation of the HPA axis results in suppression of immune function and reproductive efficiency. Cortisol also was identified as a biological marker for assessing the severity of stress in farm animals [57,3].

The energy stored in animals for production purpose is deviated from the neuroendocrine response to help the animal cope with the extremely stressful condition [58]. Neuro endocrine mechanisms are the paramount process of adaptation to various stressors [59]. The SAM axis and the HPA axis act together to stimulate and integrate all the adaptive mechanisms.

Activation of the HPA axis is a complex mechanism that involves regulation of both neuronal and endocrine regulators. Glucocorticoids play a prominent role in regulating the magnitude and duration of HPA axis activation [60,73]. When the animals are subjected to extreme heat stress condition, elevated levels of circulating glucocorticoids inhibit HPA activity at the level of the hypothalamus and pituitary. Further, the HPA axis is also subject to glucocorticoid independent regulation and the neuro-endocrine effects are also modulated by CRF binding proteins which found to be the higher concentration in the systemic circulation and in the pituitary gland [58]. Two principal neuro-endocrine adaptive mechanisms are elicited, when an animal encounters the environmental stress which includes sympathetic-adrenal-medullary (SAM) and the hypothalamic–pituitary–adrenal (HPA) axes. These axis act together which ultimately result in various stress responses encompassing the interplay of adaptive responses of various organs and receptors to overcome extreme stress condition [4,6]. Activation of the SAM axis occurs rapidly on exposure to stressful condition to stimulate the autonomic nervous system culminating in the secretion of the catecholamines adrenaline and noradrenaline [61].

The activation of the SAM and HPA axes are considered effective mechanisms to assist the animals in adapting to changes in its environment they reflect the alteration in metabolic rate, peripheral circulation, respiration, and energy availability which help the animal to survive in extreme environmental conditions [6].

Hypothalamic-Pituitary-Thyroid Axis

The hypothalamic-pituitary-thyroid axis (HPT) axis plays a critical role in the regulation of energy expenditure by affecting basal metabolic rate through the actions of thyroid hormones. The HPT axis is under the control of neurons located in the medial region of the PVN nucleus of the hypothalamus that synthesizes and release thyrotropin-releasing hormone (TRH) into the pituitary gland [62]. The TRH stimulates the release of thyrotropin (TSH) from the anterior pituitary, which in turn stimulate the synthesis and release of thyroid hormones in the target thyroid gland. Mainly two types of thyroid hormones are produced such as Triiodothyronine (T3) and Thyroxine (T4). The T3 is the main biologically active hormone recognized by its greater affinity for thyroid hormone receptors while T4 is the storage hormone which is converted to T3 by the activity of deiodinase enzymes located within most target tissues aided by the central nervous system [63]. Thyroid hormones are recognized as the key regulators of metabolic activity in domestic animals [4]. Both acute and chronic stress causes transient activation of the HPT axis. This was facilitated by the increases in TSH concentration as a result of the direct stimulatory effect of glucocorticoids on the pituitary thyrotrope [15]. However, prolonged stress is invariably associated with decreased HPT activity in farm animals in an effort to reduce the metabolic heat production during heat stress. Similarly, reduced HPT activity is mediated by glucocorticoids on TRH production in the hypothalamus [64]. Likewise, increased somatostatin secretion as a result of enhanced intrahypothalamic CRH release might also influence the reduced TSH secretion during heat stress [65]. In addition to the inhibition in TSH production, the extended activity of the HPA axis also reduces the conversion of T4 to T3 in peripheral tissues [64]. Similarly, the adipocyte hormone leptin regulates this axis by increasing TRH levels in the fed state. Leptin directly stimulates the TRH in the hypothalamic paraventricular nucleus and indirectly by regulating proopiomelanocortin neurons in the hypothalamic arcuate nucleus [66]. However, the indirect pathway is fully functional in lean animals, it is inactive during diet-induced obesity due to leptin resistance. Moreover, the primary target site for leptin that mediates its effect on the HPT axis is the arcuate nucleus, further removal of this nucleus abolishes both nutritional stress and leptin-induced regulation of the HPT axis. However, more investigations are needed in this pathway for understanding the underlying mechanisms pertaining to HPT axis in the future.

The Sympathetic-adrenal-Medullary Axis

The sympathoadrenal system consists of the adrenal glands and associated receptors. The sympathetic adrenal medullary (SAM) axis coordinates all the responses of diverse stressors by mediating the release of epinephrine from the adrenal medulla and norepinephrine from peripheral sympathetic nerves. Also, the interrelation between the central nervous system and pituitary coordinates the SAM axis activation resulting in the, release of β-endorphin which helps in circulating glucocorticoids and catecholamines to interact with a wide variety of cells to alter the metabolic and immune mechanisms [67].

Catecholamines are released to circulatory system as part of the body's stress response. It plays a pivotal role in integrating certain adaptive mechanisms, mainly the flight and fright responses [68]. The classical catecholamines includes dopamine, epinephrine and norepinephrine [69]. Additionally, catecholamines plays an enormous role in regulating the cardiopulmonary system, increasing the cardiac output, respiration rate and redistribute blood flow to the pulmonary organs, further those organs necessary for mounting responses to the various stresses [69]. The catecholamines interact with adrenergic receptors present in the cell membranes of the visceral organs and smooth muscles, further result in the activation of signaling pathways and consequent alterations of various endocrine organ functions [70]. Catecholamines are mainly circulated through blood and it could alter the effects on afferent sensory nerves impacting central nervous system function [71]. However, these rapid responses may be necessary for survival, sustained elevation of circulating catecholamines for prolonged periods of time can also produce pathological conditions, such as cardiac hypertrophy, hypertension and posttraumatic stress disorder [72].

The sympathetic component of the sympathoadrenal system comprises preganglionic neurons, where they synapse with postganglionic neurons that project and innervate the target tissues [72]. Moreover, preganglionic neurons release the neurotransmitter acetylcholine that stimulates the postganglionic neurons to release norepinephrine directly into the target tissue. In the adrenal arm of the sympathoadrenal system, preganglionic neurons extend from the spinal cord to ganglia in the adrenal medulla, where the terminals appose endocrine cells are called chromaffin cells. Acetylcholine stimulates synthesis of catecholamines in chromaffin cells in the adrenal medulla and the secretion of epinephrine and norepinephrine into the peripheral blood circulatory system. In addition, species differences were established for the level of norepinephrine and epinephrine released from the adrenal medulla [71].

Activation of brain stem noradrenergic neurons and sympathetic medullary system further contribute to the endocrine responses to various stressful stimuli. Similarly to the HPA axis, stress evoked activation of these systems promotes the mobilization of resources to compensate for adverse effects pertaining to severe stress conditions. Also, the locus coeruleus (LC) contains the largest cluster of noradrenergic neurons in the brain and innervates large segments of the neuroaxis. The LC has been implicated in a wide array of physiological and behavioral functions including emotion, vigilance, memory and various adaptive responses. Furthermore, a wide array of stressful stimuli activates LC neurons, alter their electrophysiological activity, and induce norepinephrine release [70]. Stimulation of the LC elicits several stress associated responses including ACTH release, anxiogenic like behaviors, and suppression of immune functions. In addition, there are interactions between CRF and NE neurons in the CNS. Further, central administration of CRF alters the activity of LC neurons and NE catabolism in terminal regions. Finally, dysfunction of catecholaminergic neurons in the LC has been implicated in the stress associated disorders.

Conclusion

Climate change has emerged as the major threat to the livestock production. Extended exposure of increased temperature coupled with high relative humidity compromises the ability of farm animal to control the body heat which ultimately affects their feed intake, milk production, and reproductive efficiency, resulting in severe economic constraints for dairy farmers. Therefore, understanding in depth the various adaptive responses of animals may provide future directions for coping them to the devastating effects of heat stress. Neuro-endocrine response is the principal regulator of stress response in animals and it forms the basis for regulating and coordinating all other adaptive response in domestic animals. The detailed discussions on various mechanisms and pathways associated with neuro-endocrine regulation have identified several biological markers such as cortisol, T3, T4, epinephrine, and norepinephrine. Further, in-depth understanding of the hidden intricacies of neural and endocrine regulation of adaptive responses in animals provides the scope for intervening points to protect them against the adverse impact of heat stress. There are, however, breed differences established for the level of neuroendocrine responses in various species.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

1. Stocker TF, Qin D, Plattner GK, Tignor M, Allen SK, et al. IPCC: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change (2013), pp 1535.
2. Fao I. WFP The State of Food Insecurity in the World 2013-The Multiple Dimensions of Food Security. Food and Agriculture Organization Of The United Nations. 2013.
3. Sejian V, Indu S, Naqvi SM. Impact of short term exposure to different environmental temperature on the blood

biochemical and endocrine responses of Malpura ewes under semi-arid tropical environment. Indian J Anim Scie. 2013 November;83(11):1155-1160.

4. Sejian V, Maurya VP, Naqvi SM. Adaptive capability as indicated by endocrine and biochemical responses of Malpura ewes subjected to combined stresses (thermal and nutritional) in a semi-arid tropical environment. Int J Biometeorol. 2010 Nov;54(6):653-661.
5. Shinde AK, Sejian V. Sheep husbandry under changing climate scenario in India: An overview. Indian Journal of Animal Science. 2003;83:998-1008.
6. Niyas PAA, Chaidanya K, Shaji S, Sejian V, Bhatta R, et al. Adaptation of livestock to environmental challenges. J Vet Sci Med Diagn. 2015;4:3.
7. Fedoroff NV, Battisti DS, Beachy RN, Cooper PJ, Fischhoff DA, et al. Radically rethinking agriculture for the 21st century. Science. 2013;327:833-834.
8. Hulme PE. Adapting to climate change: is there scope for ecological management in the face of a global threat. J of Applied Ecology. 2005;42:784-794.
9. Brown-Brandl TM, Eigenberg RA, Hahn GL, Nienaber JA, Mader TL, et al. Analyses of thermoregulatory responses of feeder cattle exposed to simulated heat waves. Int J Biometeorol. 2005;49:285-296.
10. Thornton PK. Livestock production: recent trends, future prospects. Philos Trans R Soc Lond B Biol Sci. 2010;365(1554):2853-2867.
11. Joy A, Pragna P, Archana PR, Sejian PR, Bagath M. Significance of Metabolic Response in Livestock for Adapting to Heat Stress Challenges. Asian Journal of Animal Sciences. 2016;10:224-234.
12. Chen P, Van Hover C, Lindberg D, Li C. Central urocortin 3 and type 2 corticotropin-releasing factor receptor in the regulation of energy homeostasis: critical involvement of the ventromedial hypothalamus. Front Endocrinol. 2013;3:180-192.
13. Nardone A, Ronchi B, Lacetera N, Ranieri MS, Bernabucci U. Effects of climate changes on animal production and sustainability of livestock systems. Livestock Science. 2010;130:57-69.
14. Collier RJ, Renquist BJ, Xiao YA. 100-Year Review: Stress physiology including heat stress. J Dairy Sci. 2017;100:10367-10380.
15. Shaji S, Sejian V, Bagath M, Manjunathareddy GB, Kurien EK, et al. Summer season related heat and nutritional stresses on the adaptive capability of goats based on blood biochemical response and hepatic HSP70 gene expression. Biological Rhythm Research. 2016;48:65-83.
16. Indu S, Sejian V, Naqvi SM. Impact of simulated heat stress on growth, physiological adaptability, blood metabolites and endocrine responses in Malpura ewes under semiarid tropical environment. Animal Production Science. 2014;55:1314-1323.
17. Taylor NA, Tipton MJ, Kenny GP. Considerations for the measurement of core, skin and mean body temperatures. J Thermal Bio. 2014;46:72-101.
18. Etim NN, Williams ME, Akpabio U, Offiong EE. Haematological parameters and factors affecting their values. Agricultural Science. 2014;2:37-47.
19. Salin K, Auer SK, Rey B, Selman C, Metcalfe NB. Variation in the link between oxygen consumption and ATP production, and its relevance for animal performance. In Proceedings of Royal Society of London. 2015; 282:20151028.
20. Glitz KJ, Seibel U, Rohde U, Gorges W, Witzki A, et al. Reducing heat stress under thermal insulation in protective clothing: microclimate cooling by a 'physiological'method. Ergonomics. 2015;58:1461-1469.
21. Benitez Dorta V, Caballero MJ, Betancor MB, Manchado M, Tort L, et al. Effects of thermal stress on the expression of glucocorticoid receptor complex linked genes in Senegalese sole (Solea senegalensis): Acute and adaptive stress responses. Gen Comp Endocrinol. 2017;252:173-185.
22. Simons RL, Klopack ET. Invited Address:"The Times They Are A-Changin'" Gene Expression, Neuroplasticity, and Developmental Research. J Youth Adolesc. 2015;44:573-580.
23. Srikanth K, Kwon A, Lee E, Chung H. Characterization of genes and pathways that respond to heat stress in Holstein calves through transcriptome analysis. Cell Stress and Chaperones. 2017;22:29-42.
24. Pockley AG, Henderson B Extracellular cell stress (heat shock) proteins—immune responses and disease: an overview. Philos Trans R Lond B Bio Sci. 2018;373:20160522.
25. Gaughan JB, Bonner SL, Loxton I, Mader TL. Effects of chronic heat stress on plasma concentration of secreted heat shock protein 70 in growing feedlot cattle. J Anim Sci. 2013;91:120-129.
26. Sejian V, Bhatta R, Gaughan J, Malik PK, Naqvi SMK Lal R. Adapting sheep production to changing climate: conclusions and researchable priorities. In: Sheep production adapting to climate change. Sejian V, Bhatta R, Gaughan J, Malik PK, Naqvi SMK, Lal R (Eds), Springer-Verlag GMbH Publisher, Singapore, pp 431-441.
27. Muráni E, Ponsuksili S, D'Eath RB, Turner SP, Kurt E, et al. Association of HPA axis-related genetic variation with stress reactivity and aggressive behaviour in pigs. BMC Genet. 2010;11:74.
28. Mahesh G, Kumar S, Dangi SS, Jangir BL. Physiological, biochemical and molecular responses to thermal stress in goats. Int J Livest Res. 2013;3:27-38.
29. Sejian V, Maurya VP, Naqvi SM. Adaptability and growth of Malpura ewes subjected to thermal and nutritional stress. Tropical Animal Health and Production. 2010;42:1763-1770.
30. Sheriff MJ, Dantzer B, Delehanty B, Palme R, Boonstra R. Measuring stress in wildlife: techniques for quantifying glucocorticoids. Oecologia. 2011;166:869-887.
31. Mostl E, Palme R. Hormones as indicators of stress. Domestic Animal Endocrinology. 2002;23:67-74.
32. Sharma S, Ramesh K, Hyder I, Uniyal S, Yadav VP, et al. Effect of melatonin administration on thyroid hormones, cortisol and expression profile of heat shock proteins in goats (Capra hircus) exposed to heat stress. Small Ruminant Research. 2013;112:216-223.
33. Reiter, Russel J. Melatonin: the chemical expression of darkness. Molecular and Cellular Endocrinology. 1991;79:153-158.
34. Abecia JA, Forcada F, González-Bulnes A. Hormonal control of reproduction in small ruminants. Animal Reproduction Science. 2012;130:173-179.
35. Bagath M, Sejian V, Archana SS, Manjunathareddy GB, Parthipan S, et al. Effect of dietary intake on somatotrophic axis–related gene expression and endocrine profile in Osmanabadi goats. Journal of Veterinary Behavior: Clinical Applications and Research. 2016;13:72-79.
36. Pavani K, Carvalhais I, Faheem M, Chaveiro A, Reis FV, et al. Reproductive performance of Holstein dairy cows grazing in dry-summer subtropical climatic conditions: effect of heat stress and heat shock on meiotic competence and in vitro fertilization. Asian-Australas J Ani Sci. 2015;28:334-342.
37. Baumgard LH, Rhoads Jr RP. Effects of heat stress on postabsorptive metabolism and energetics. Annual Review of Animal Bioscience. 2013;1:311-337.
38. Itai M, Kuwano Y, Nishikawa T, Rokutan K, Kensei N. Geranylgeranylacetone prevents stress-induced decline of leptin secretion in mice. J Med Invest. 2018;65:103-109.
39. Spencer RL, Deak TA. A users guide to HPA axis research. Physiology and Behavior. 2017;178:43-65.
40. Lloyd RB, Nemeroff CB. The role of corticotropin-releasing hormone in the pathophysiology of depression: therapeutic implications. Current Topics in Medicinal Chemistry. 2011;11:609-617.
41. Nader N, Chrousos GP, Kino T. Interactions of the circadian CLOCK system and the HPA axis. Trends Endocrinol Metab. 2010;21:277-286.
42. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent

developments and mechanistic insights. Mol Cell Endocrinol. 2011;335:2-13.

43. Grammatopoulos DK. Insights into mechanisms of corticotropin-releasing hormone receptor signal transduction. British Journal of Pharmacology. 2012;166:85-97.
44. Regev L, Baram TZ. Corticotropin releasing factor in neuroplasticity. Frontiers in Neuroendocrinology. 2014;35:171-179.
45. Toth M, Gresack JE, Hauger RL, Halberstadt AL, Risbrough VB. The role of PKC signaling in CRF-induced modulation of startle. Psychopharmacology. 2013;229:579-589.
46. Stengel A, Tache YF (2014) CRF and urocortin peptides as modulators of energy balance and feeding behavior during stress. Frontiers in Neuroscience. 2014;8:52.
47. Stricker EM, Verbalis JG. Water and salt intake and body fluid homeostasis. In Fundamental Neuroscience. 2013;4:783-797.
48. Goel N, Workman JL, Lee TT, Innala L, Viau V. Sex differences in the HPA axis. Comprehensive Physiology. 2014;4:1121-1155.
49. Wingfield JC. Ecological processes and the ecology of stress: the impacts of abiotic environmental factors. Functional Ecology. 2013;27:37-44.
50. Cain DW, Cidlowski JA. Specificity and sensitivity of glucocorticoid signaling in health and disease. Best Practice and Research: Clinical Endocrinology and Metabolism. 2015;29:545-556.
51. Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Comprehensive Physiology. 2016; 6:603-621.
52. Aguilera G. Stress Adaptation and the Hypothalamic-Pituitary-Adrenal Axis. Molecular Neuroendocrinology: From Genome to Physiology. 2016;24:375-403.
53. Renaudeau D, Collin A, Yahav S, De Basilio V, Gourdine JL, et al. Adaptation to hot climate and strategies to alleviate heat stress in livestock production. Animal. 2012;6:707-728.
54. Besedovsky HO, Del Rey A. Central and peripheral cytokines mediate immune-brain connectivity. Neurochemical Research. 2011;36:1-6.
55. Touma C, Palme R. Measuring fecal glucocorticoid metabolites in mammals and birds: the importance of validation. Annals of the New York Academy of Sciences. 2005;1046:54-74.
56. Nejad JG, Lohakare JD, Son JK, Kwon EG, West JW, et al. Wool cortisol is a better indicator of stress than blood cortisol in ewes exposed to heat stress and water restriction. Animal. 2014;8:128-132.
57. Gądek-Michalska A, Tadeusz J, Rachwalska P, Bugajski J. Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems. Pharmacol Rep. 2013;65:1655-1662.
58. Volden PA, Conzen SD. The influence of glucocorticoid signaling on tumor progression. Brain Behav, Immun. 2013;30:26-31.
59. Sunil Kumar BV, Ajeet K, Meena K. Effect of heat stress in tropical livestock and different strategies for its amelioration. Journal of Stress Physiology and Biochemistry. 2011;7:45-54.
60. Hill MN, Tasker JG. Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. Neuroscience. 2012;204:5-16.
61. Verbrugghe E, Boyen F, Gaastra W, Bekhuis L, Leyman B, et al. The complex interplay between stress and bacterial infections in animals. Vet Microbiol. 2012;155:115-127.
62. Fekete C, Lechan RM. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. Endocr Rev. 2013;35:159-194.
63. Thomas C, Pellicciari R, Pruzanski M, Auwerx J, Schoonjans K. Targeting bile-acid signalling or metabolic diseases. Nat Rev Drug Discov. 2008;7:678-693.
64. Uribe RM, Cisneros M, Vargas MA, Lezama L, Cote-Vélez A, et al. The systemic inhibition of nitric oxide production rapidly regulates TRH mRNA concentration in the paraventricular nucleus of the hypothalamus and serum TSH concentration. Studies in control and cold-stressed rats. Brain Res. 2011;1367:188-197.
65. Papadimitriou A, Priftis KN. Regulation of the hypothalamic-pituitary-adrenal axis. Neuroimmunomodulation. 2009;16:265-271.
66. Perello M, Çakir I, Cyr NE, Romero A, Stuart RC, et al. Maintenance of the thyroid axis during diet-induced obesity in rodents is controlled at the central level. Am J Physiol Endocrinol Metab. 2010;299:976-989.
67. De Castro ED, Lopez I, Cortes B, Pineda C, Garfia B, et al. Influence of feeding status, time of the day, and season on baseline adrenocorticotropic hormone and the response to thyrotropin releasing hormone-stimulation test in healthy horses. Domest Anim Endocrinol. 2014;48:77-83.
68. Palkovits M. Catecholamines and stress. Clinical Neuroscience. 2014;67:89-93.
69. McMorris T. Developing the catecholamines hypothesis for the acute exercise-cognition interaction in humans: lessons from animal studies. Physiology and Behavior. 2016;165:291-299.
70. Ippoliti F, Canitano N, Businaro R. Stress and obesity as risk factors in cardiovascular diseases: a neuroimmune perspective. J Neuroimmune Pharmacol. 2013;8:212-226.
71. Yarandi SS, Peterson DA, Treisman GJ, Moran TH, Pasricha PJ. Modulatory effects of gut microbiota on the central nervous system: how gut could play a role in neuropsychiatric health and diseases. J Neurogastroenterol Motil. 2016;22:201-212.
72. Roy SJ, Prince PS. Protective effects of sinapic acid on cardiac hypertrophy, dyslipidaemia and altered electrocardiogram in isoproterenol-induced myocardial infarcted rats. Eur J Pharmacol. 2013;699:213-218.
73. Ralph CR, Tilbrook AJ. INVITED REVIEW: The usefulness of measuring glucocorticoids for assessing animal welfare. J Anim Sci. 2016;94:457-470.