The importance of hypothalamic-pituitary (HP) interactions in mammals is well recognized. In health, this highly regulated and integrated system is involved in the homeostasis of intermediary metabolism, immune responses, body temperature, hunger, thirst, growth, reproduction, and cardiovascular function, to name a few functions. The hypothalamus coordinates many hormonal and behavioral circadian rhythms and complex neuroendocrine inputs/outputs and behaviors, including level/content of consciousness, mood, instinctive behaviors (eg, maternal), and feeding.

The HP axis is critical for evoking the biologic responses to internal and external stressors, where activation of both the HP axis and sympathetic nervous systems results in adrenocortical and adrenomedullary secretion of corticosteroids and catecholamines, respectively. These biologically active messengers modulate important responses, such as heightened alertness, glucose mobilization/use, vasomotor tone, cardiac output to improve delivery of metabolic fuel (notably glucose and oxygen), and removal of metabolic waste (lactic acid and carbon dioxide) during times of physiologic and pathologic stress. Like many biologic systems, there is a limit and capacity for these responses to work and when they are reached or exceeded, HP axis dysfunction results in serious compromises that can lead to increased morbidity and mortality.

Dysfunctions of any of the multiple HP axes can modify many physiologic functions and, if severe, can be life threatening. Individual and species differences exist regarding HP activation, stimulation, hormonal secretion, and effector organ responses. Disorders of the hypothalamic-pituitary-adrenal axis (HPAA) are better described in the human and comparative literature, with a paucity of available information in the horse. In humans, HPAA dysregulation related to sepsis/septic shock, traumatic central diabetes insipidus, and syndrome of inappropriate antidiuretic hormone secretion (SIADH) are examples of diseases that affect one or more components of the HP system. Although the HPAA has been the most studied HP axis in the horse, when compared with other species, available information is lacking.
The focus of this article is primarily on the anatomy, physiology, and pathophysiology of the HPAA in horses with emphasis on arginine vasopressin (AVP), corticotropin-releasing hormone (CRH) (or corticoliberin), and their downstream response by the pituitary and adrenal glands. A discussion of the HP response to critical illness of humans and animals, from experimental and clinical research, is provided. Other HP axes include the hypothalamic-pituitary-thyroid (HPT) axis with thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) and the hypothalamic-pituitary growth hormone (GH) axis with growth hormone–releasing hormone (GHRH) and GH. HP axes involved in reproduction are not discussed. Pathologic conditions associated with HPT and GH axes relevant to energy metabolism and skeletal development are discussed by Barsnick elsewhere in this issue. A complete discussion of the adrenal gland and its interactions with the hypothalamus and pituitary gland in health and disease can be found in the article by Hart and Barton elsewhere in this issue. Similarly, the article by McFarlane includes a thorough discussion of pituitary pars intermedia dysfunction (PPID).

ANATOMY

The hypothalamus, located in the ventral diencephalon, is a complex anatomic and organizational structure, with many nuclei (preoptic, supraoptic, paraventricular, anterior, suprachiasmatic, dorsomedial, ventromedial, and arcuate nuclei) and areas involved with control of body temperature, energy metabolism, blood pressure regulation (water and sodium), stress response, reproduction, and environment integration. The hypothalamus is highly connected to other higher structures of the central nervous system (eg, limbic system) and with the pituitary gland downstream. Because of its unconscious and regulatory functions, the hypothalamus is a major component of the autonomic nervous system.

In vertebrates, the pituitary gland is divided into 3 distinct lobes: pars nervosa (neurohypophysis or posterior pituitary), pars intermedia (intermediate lobe), and pars distalis (adenohypophysis or anterior pituitary), each having a unique role in endocrine homeostasis. In the equine species, the adenohypophysis surrounds the other pituitary lobes.

Hypothalamic neuroendocrine neurons control pituitary gland function. Magnocellular neurons in the paraventricular and supraoptic nuclei synthesize AVP and oxytocin, which are transported (hypothalamic-hypophyseal tract) by unmyelinated axons and stored in secretory vesicles in the nerve terminals (Herring bodies) in the neurohypophysis. Parvocellular neurons in various hypothalamic nuclei make direct connection to blood vessels in the median eminence (hypothalamic-hypophyseal portal system) to release factors that control the synthesis and secretion of hormones by the adenohypophysis. These hypothalamic factors include CRH, TRH, and AVP. Although the median eminence is part of the central nervous system, it is strategically located outside the blood-brain barrier to mediate a rapid pituitary response to factors present in portal and systemic circulation.

Neurons from other hypothalamic nuclei and areas (arcuate nucleus and preoptic area) also connect to the portal system to regulate hormones involved with somatic, metabolic, and reproductive functions, including GHRH to release GH, TRH to increase TSH and prolactin release, gonadotropin-releasing hormone to increase follicle-stimulating hormone and luteinizing hormone secretion, somatostatin to inhibit GH secretion, and dopamine (DA) to inhibit prolactin.
and TSH release. Reproductive hormones are not discussed in this review. The cells of the pars intermedia are primarily controlled by hypothalamic TRH stimulation and dopaminergic inhibition (see the article by McFarlane elsewhere in this issue).

**HPAA DYNAMICS**

The HPAA responses are essential for life and have been investigated in the equine fetus, preterm foal, and neonatal foal. In healthy, term foals, increases in AVP; adrenocorticotropic hormone (ACTH), also known as corticotropin or adrenocorticotropic; and cortisol concentrations occur as a physiologic adaptation to hypovolemia and hypotension, indicating that at birth foals have a functional HPAA.

The secretion of inhibitory or stimulatory endocrine factors by a higher endocrine center (hypothalamus) controls the response of its target organ (pituitary gland), which releases hormones with various critical functions. In addition, these hormones inhibit (negative feedback) or stimulate (positive feedback) the higher controlling center to create an endocrine homeostatic system.

Stimulation of the HP axis starts with excitation of the hypothalamus by different inputs. CRH and AVP are released into the pituitary portal system to increase ACTH secretion by the pituitary corticotrophs. AVP is considered the main secretagogue for ACTH in adult horses, late-term equine fetuses, and foals. AVP is also responsible for the short-term fluctuations in ACTH concentrations. This has been confirmed in exercising horses where CRH seemed to play a minor regulatory role on ACTH secretion. ACTH in turn controls the secretion of cortisol by the adrenal cortex (zona fasciculata). Cortisol has direct and indirect pathways to negatively feedback on the hypothalamus, limbic system, and pituitary gland. This attenuates or decreases the release of CRH, AVP, and ACTH. It seems that the glucocorticoid negative feedback effect on AVP secretion is less robust than that for CRH because AVP secreting neurons are less sensitive to glucocorticoids. Therefore, the reciprocal interactions among CRH, AVP, ACTH, and cortisol, rather than one signaling hormone, modulate HPAA dynamics.

Recently, Keenan and colleagues described the complex feedback and feed-forward interactions between AVP, CRH, ACTH, and cortisol in healthy horses. Simply stated, they showed that hypocortisolemia amplifies CRH and AVP secretion when mean cortisol feedback concentrations decrease 0% to 25% and both CRH and AVP synergize in evoking ACTH secretion. There was also an autostimulation/autoinhibition mechanism for the hypothalamic peptides independent of cortisol concentration, where reduced feedback by CRH of 0% to 25% and AVP by 50% augments both CRH and AVP secretion.

ACTH binds receptors in the adrenal gland cortex to stimulate steroid synthesis and secretion via the adenylate cyclase second messenger system. In the mitochondria, cholesterol is converted to pregnenolone. Through the action of 3β-hydroxysteroid dehydrogenase and 17α-hydroxylase, pregnenolone is biotransformed to progesterone and 17α-hydroxyprogesterone, the precursors of aldosterone and cortisol, respectively. The principle function of ACTH is to stimulate cortisol release and, to a lesser extent, also aldosterone.

In addition to its function in the adenohypophysis, AVP is transported through the hypothalamic-neurohypophyseal tract to the neurohypophysis to be released in systemic circulation to act on the renal collecting ducts to retain water and on smooth muscle cells of the vasculature to induce constriction.
HORMONES

Corticotropin-Releasing Hormone

In horses, CRH is a 41-amino acid peptide derived from a 195-amino acid preprohormone (196 amino acids in humans and dogs). CRH is synthesized by parvocellular neurons in the paraventricular nucleus of the hypothalamus and released by neurosecretory terminals into the primary capillary plexus of the HP portal system to stimulate ACTH secretion. Factors that affect CRH release include stress and cortisol concentrations. CRH is also produced by the placenta in late gestation where it seems to determine pregnancy length and parturition.

Arginine Vasopressin

AVP is a 9-amino acid peptide synthesized by the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. Because AVP has a short half-life in humans (5–15 minutes), blood concentrations reflect recent hormonal release. AVP has several physiologic functions, including water reabsorption by renal collecting tubules and vasoconstriction. Major stimuli for AVP secretion are controlled by osmotic and nonosmotic factors. Plasma hypertonicity stimulates hypothalamic osmoreceptors to release AVP. This system is very sensitive and increases in plasma tonicity of 1% to 2% can induce AVP release. Volume depletion (hypotension) is sensed by baroreceptors in the left atrium, aortic sinus, and carotid sinus. A decrease in blood volume of 5% to 10% results in rapid AVP release.

Growth Hormone–Releasing Hormone and Somatostatin

GHRH is a neurosecretory hormone of the hypothalamic arcuate nucleus that is transported to the adenohypophysis to stimulate release of GH. GHRH stimulates GH release through interaction with the GHRH receptor on somatotrophs via Gs-protein/cyclic adenosine monophosphate and inositol triphosphate/diacylglycerol signal transduction. GHRH is secreted in a pulsatile manner and of critical importance for postnatal growth, bone growth, and intermediary metabolism.

Somatostatin, or GH inhibitory hormone, is a peptide produced by hypothalamic neurons as well as cells in the stomach, intestine, and pancreas. Similar to GHRH, somatostatin is released into the HP portal system and its main function is to inhibit the secretion of GH and TSH. Somatostatin and insulinlike growth factor 1 are the main components of the negative feedback system for GH release.

Thyrotropin-Releasing Hormone

TRH is synthesized by neurons of the paraventricular nucleus from a polypeptide precursor that is cleaved by proteases to the active tripeptide hormone. TRH stimulates the secretion TSH (thyrotropin) by the pituitary thyrotrophs. In turn, TSH increases thyroid hormone release from the thyroid gland. Increased metabolic demand and metabolic rate activate the HPT axis, leading to increases in TRH, TSH, and thyroid hormones. TRH also acts in other pituitary cell types. For example, TRH stimulates the secretion of prolactin by the lactotrophs, ACTH by the corticotrophs, and GH by the somatotrophs. In the melanotrophs of the pars intermedia, TRH promotes the synthesis and secretion of proopiomelanocortin (POMC) peptide, in particular ACTH. These effects seem to be primarily mediated by the TRH’s ability to decrease DA secretion. DA is a cell inhibitory factor in the pituitary pars distalis and pars intermedia. TRH release is suppressed by TSH, thyroid hormones (endogenous and exogenous) and glucocorticoid (endogenous and exogenous) through a negative feedback system.
**Dopamine**
The functions of DA in the pituitary gland are by far inhibitory. Dopaminergic neurons, also known as tuberoinfundibular DA neurons, are primarily located in the arcuate nucleus of the hypothalamus. Axons from tuberoinfundibular DA neurons project into the HP portal system to inhibit prolactin, GH, and TSH secretion. These neurons also make contact with melanotrophs in the pars intermedia to inhibit the synthesis and secretion of POMC peptides, including ACTH and α-melanocyte–stimulating hormone (α-MSH). Basic knowledge of the dopaminergic system is important to understand the pathogenesis of equine PPID, tall fescue toxicosis, and their treatment.

**Proopiomelanocortin**

POMC is a precursor polypeptide with 267 amino acid residues. The POMC gene encodes a polypeptide hormone precursor that undergoes extensive, tissue-specific, post-translational processing via cleavage by subtilisin-like enzymes (prohormone convertases). There are 8 potential cleavage sites within the polypeptide precursor, and, depending on tissue type and the available convertase, processing may yield as many as 10 biologically active peptides involved in diverse cellular functions. POMC is primarily expressed in the corticotrophs of the pars distalis and melanotrophs of the pars intermedia. POMC processing differs between the pars distalis and pars intermedia of horses. ACTH, beta-lipotropic hormone (β-LPH), gamma-lipotropic hormone (γ-LPH), and β-endorphin (β-END) are the main peptides in the pars distalis, whereas ACTH, β-LPH, and α-MSH are primarily produced in the pars intermedia. ACTH undergoes further cleavage to yield additional active hormones (see discussion of ACTH later).

**Adrenocorticotropic Hormone**

ACTH is a 39-amino acid peptide produced in the pituitary pars distalis from post-translational processing of POMC. ACTH main function is to stimulate glucocorticoid production by the adrenal cortex. ACTH is metabolized to ACTH1-13, which is identical to α-MSH. Corticotropin-like peptide is another major ACTH metabolite, which represents ACTH18-39. α-MSH, β-LPH, and corticotropin-like peptide are the main fragments in the pars intermedia, with ACTH production being minimal. DA has inhibitory effects on the synthesis and secretion of POMC peptides, including ACTH. DA agonists are used to decrease ACTH production in horses with PPID.

**β-Endorphin**

β-END is a 31-amino acid peptide generated from cell-specific cleavage of POMC. It is an agonist of various endogenous opioid receptors (μ1, 2, 3; δ1, 2; and κ1, 2, 3), but μ1 is considered the main receptor by which β-END (and morphine) mediates analgesia, sedation, and narcosis.

**α-Melanocyte-Stimulating Hormone**

α-MSH is a post-translational product of POMC cleavage in the pars intermedia. It has important roles in the regulation of appetite and sexual behavior, and it is a prime regulator for melanin production by melanocytes in skin and hair. Plasma α-MSH has been measured in horses in the context of diagnosing pars intermedia dysfunction (Cushing disease) and, like ACTH, its concentrations are affected by season.
RECEPTORS

AVP exerts its effects through 5 potential receptors, named V₁, V₂, V₃, oxytocin-receptor, and a purinergic (P₂) receptor. These are G-protein transmembrane receptors found in specific tissues. In horses, the 3 AVP receptors are the likely mediators of the responses to endogenous and exogenous AVP and analogs.

V₁

These receptors mediate the pressor actions of AVP on vascular smooth muscle. V₁ receptors are also located in the liver, testis, brain, and renal medulla. V₁ receptor agonism activates G_{q/11} protein signaling, leading to the release of second messengers (inositol triphosphate and diacylglycerol), which in turn activate protein kinase C to increase intracellular calcium flux.¹⁹ This sequence of events increases vasomotor tone and vasoconstriction.

V₂

These receptors are located in the renal collecting ducts. Through cyclic adenosine monophosphate signaling, V₂ receptor activation increases the translocation of aquaporin-2 channels from intracellular vesicles into the cell membrane of the tubular epithelial cells. Without the effect of AVP, urinary osmolality can be as low as 50 mOsm/L by continued sodium reabsorption without water reabsorption.²⁰ Other effects include increasing von Willebrand factor production and release from endothelial stores.

V₃

V₃ receptors (also termed V₁b receptors) are primarily located in the corticotrophs of the adenohypophysis and upon AVP stimulation there is a rapid release of ACTH into systemic circulation.

CRH Receptors

Two types of CRH receptors have been identified, namely CRH-1 and CRH-2. CRH-1 is the main receptor in s populating the pituitary corticotrophs and its activation increases POMC expression and ACTH production.

TRH Receptors

TRH receptors are present in the thyrotrophs and lactotrophs of the pars distalis and melanotrophs in the pars intermedia.

TSH Receptors

Receptors for TSH are primarily located in the follicular cells of the thyroid gland where, on activation, lead to increased synthesis of triiodothyronine and thyroxine.

TESTING THE HYPOTHALAMIC-PITUITARY AXIS

Testing of HP function can be done by measuring hormonal concentrations or by performing dynamic tests. Hormone concentrations can be measured in systemic venous blood, pituitary venous blood, saliva, and urine.²¹ Determination of systemic blood hormone concentrations is the most commonly used method. Many hormones are released in small amounts (eg, pg/dL to ng/dL), have similar amino acid sequences (eg, AVP and oxytocin), or are different between species. Therefore, to determine their blood concentrations, sensitive and specific methods, such as radioimmunoassays, immunoradiometric assays, immunochemiluminometric assays, and ELISAs, are
used. Be aware that there are species differences between hormones and that assay validation is necessary before making any interpretation of the data. Measurement of AVP and other small peptides requires appropriate sample handling and expedient analysis because plasma proteases may result in hormone degradation in vitro. Several studies advocate the use of protease inhibitors, such as aprotinin, to preserve sample integrity especially when processing may be delayed.

Assessing HP or HPAA function generally requires stimulation or suppression of the axis via the administration of a specific hormone. For example, ACTH administration stimulates the zona fasciculata to secrete cortisol, where ACTH is the administered stimulator and cortisol is the target organ measured response. This indicates an actual response to provocation, which is superior to single random sample hormone concentration determinations in the assessment of axis functionality. A thorough discussion of the methodology, utility, and pitfalls of the ACTH and TRH stimulation tests is covered in the articles by Breuhaus and McFarlane elsewhere in this issue.

A well-accepted test for assessing the HPAA in humans is the CRF (corticorelin) challenging test. In addition, this test is for differentiating whether or not high blood ACTH concentrations are from the pituitary gland or an ectopic source. A recent study in horses evaluated the effect of ovine CRH on plasma and salivary total cortisol responses and found that for the same challenge dose of ovine CRH, salivary cortisol concentrations peaked 5 times higher compared with baseline whereas plasma cortisol concentrations increased up to 1.5 times higher compared with baseline. The CRH stimulation test has been used in calves with chronic activation of the HPAA as a result of external stressors.

Some investigators believe that salivary cortisol concentrations are more reflective of biologically active systemic cortisol concentrations because only unbound (free) cortisol can diffuse into saliva and may have utility in HPAA function testing in horses.

Another test of pituitary function is the TRH stimulation test where exogenous TRH is administered and the expected response should be an increase in TSH from the thyrotrophs of the pars distalis. Exogenous TRH also stimulates ACTH secretion by the melanotrophs of the pars intermedia and this finding has been used to aid in the diagnosis of PPID. More recently, the TRH stimulation test was assessed in horses with anhidrosis where anhidrotic horses had different TSH responses to TRH stimulation than normal horses. There was no difference in thyroid hormone concentrations between horses and, as such, the biologic significance of an altered pituitary (TSH) response is unknown.

HYPOTHALAMIC-PITUITARY DYSFUNCTION IN CRITICAL ILLNESS

Human Perspective

Disorders of HP axes with emphasis on hypothalamic dysfunction are better described in humans than in veterinary patients. Endocrinopathies of critical illness, including those related to critical illness related corticosteroid insufficiency (CIRCI), also known as relative adrenal insufficiency (RAI); diabetes insipidus (DI) (central and nephrogenic); SIADH; and many heritable conditions are examples that are described. Conversely, although the body of evidence is being gathered in equine patients, in particular those afflicted with critical illness, many of these clinical conditions are by and large poorly understood, poorly defined, and/or poorly recognized if they exist. Dysfunction of the HPAA is better understood in septic and critically ill foals, largely through prospective multicenter research endeavors, and further investigation is ongoing.
In people, HPAA dysfunction is becoming increasingly recognized. For specific patient populations, hormonal/peptide supplementation, including AVP and cortisol (and their analogs), is used as therapy. Notable are patients with septic shock, defined as patients with severe sepsis and refractory hypotension despite fluid resuscitation. The 2008 Surviving Sepsis Campaign guidelines illustrate the usefulness of these treatments in providing hemodynamic support, among many other therapeutics, to improve survival in septic human patients.31

Changes in AVP and ACTH have been well documented in humans,32 including children33 and adults with early sepsis.34 Alterations seemingly follow a pattern of having an increase in AVP, ACTH, and cortisol during the acute early stages of sepsis and with prolonged stimulation, followed by decreases of these same hormones occurring proportionally to the magnitude of disease severity and/or duration of disease. Increases in plasma AVP concentrations have been found in baboons, dogs,35 rats,9 and foals.28 In children with acute septic shock, nonsurvivors are reported to have increased AVP concentrations.33 Proposed mechanisms for the increased AVP concentration during sepsis include a physiologic response to stress,6 changes in blood pressure6,33,36 and blood volume in relation to blood pressure,6,33 changes in serum osmolality,16,19,33 and response to circulating endotoxin and proinflammatory mediators, including IL-1β, IL-6, and tumor necrosis factor (TNF)-α.8,33,37,38 Moreover, in fulminant septic shock, AVP concentrations have been shown to be lower than anticipated for the degree of critical illness.39 As the shock state progresses, the early increased AVP concentrations decrease to normal or subnormal values despite a lack of resolution or even worsening of a patient’s clinical condition. This has been called relative vasopressin deficiency because in the presence of hypotension, vasopressin is expected to be elevated.34 The author and coworkers have evidence that a similar phenomenon may occur in septic foals (discussed later).

In light of these observations in humans, AVP is administered as an adjunctive pressor agent after volume resuscitation, inotropes (eg, dobutamine), and first-line pressors, such as norepinephrine. Primary use of AVP for refractory hypotension alone or in high doses is not recommended due to concerns of coronary and splanchnic ischemia and conflicting efficacy findings.40,41 To date, large protocol driven trials investigating the use of AVP or cortisol administration in critically ill veterinary patients are lacking. Infrequent and sparse case reports/case series have been reported.42–44 Given the surfeit of research, investigation, and success in the human critical care field, however, the therapeutic utility of AVP and/or cortisol supplementation deserves more investigation in critically ill foals and adult horses.

Information on other endocrine axes in critical illness is provided in the article by Toribio elsewhere in this issue.

Animal Studies

There are few studies that have investigated the clinical utility of AVP or AVP analogs for the treatment of hypotension, either as single therapy or in combination with other inotrope or vasopressor agents. One of the significant negative effects of AVP use in septic patients is its ability to shunt blood flow from the skin and splanchnic circulation to other vital organs. Splanchnic perfusion is vital to maintain intestinal integrity, and when significant hypoperfusion occurs, this is permissive for bacterial translocation, bacteremia, systemic inflammatory response syndrome (SIRS), and sepsis. In a study of isoflurane-induced hypotension in foals, AVP administration decreased splanchnic perfusion in excess of that caused by systemic hypotension and to a greater extent than other vasoactive substances, including dobutamine and norepinephrine.45
Similarly, in a porcine model of endotoxemia, cutaneous and splanchnic microcirculation measured by microsphere flow was depressed after the administration of AVP and was not improved when dobutamine was coadministered.46

**Vasopressin Use in Horses**

The use of vasopressin as a therapeutic in horses is poorly documented in clinical practice. Some clinicians use vasopressin (0.25–8 mU/kg/min) as a continuous rate of infusion to treat catecholamine-refractory hypotension in endotoxemia/sepsis of adult horses and foals with variable results. Given the lack of evidence for its use in septic foals, it is prudent to consider AVP when other pressors and intropes have failed. Also, for similar reasons, starting at a low dose and gradually titrating up is a recommended safe practice when using vasoactive substances.

AVP is used in people for cardiopulmonary cerebral resuscitation (0.2–0.8 U/kg) as a first-line treatment or when epinephrine has failed to yield return of spontaneous circulation.17 This treatment recommendation might also have utility in resuscitation of critically ill foals. AVP was approximately a 5 times more potent vasopressor in rats and human subjects with septic shock/endotoxemia than in normal subjects.47,48 Reasons for this effect may be due in part to the ability of AVP to reset ATP-sensitive potassium channels, potentiate endogenous catecholamines, and inhibit inducible nitric oxide synthase.49

**Equine Perspective**

There are few reports investigating the pathophysiology or treatment of HP dysfunction in horses. Most studies are observational and physiologic in nature, assessing the normal HP axis (and HPAA) response or interaction.1,6,28,50,51 Recently, Wong and colleagues51 published normal values for AVP in foals during the first 3 months of life, with minimal changes over time (6.2 ± 2.5 pg/mL). These values were similar to those previously reported in healthy foals.28

**Critical Illness (Endotoxemia and Sepsis)**

Endotoxemia and sepsis are frequent findings in adult horses and foals, respectively. Studies have shown that bacterial toxins (exotoxins and endotoxin) can induce activation of the mononuclear phagocyte system and the production of proinflammatory cytokines in septic foals,52,53 notably TNF-α, interleukin (IL)-1β, and IL-6, which are thought to be responsible, in part, for the development of systemic inflammation and the progression to SIRS. Endotoxin and proinflammatory cytokines themselves also are AVP secretagogues in humans16,37 and horses8 by activating AVP magnocellular neurons. TNF-α is an early mediator in endotoxemia and is correlated with the severity of clinical signs.52–54 Similarly, detectable endotoxin concentrations in plasma of septic foals are correlated with nonsurvival.52

In a prospective study of 111 neonatal foals (septic n = 51, sick nonseptic n = 29, and healthy n = 31), septic foals, determined by clinical findings, blood culture status, and/or sepsis score greater than or equal to 14, had increases in plasma AVP, ACTH, and cortisol concentrations. The median age was 24 hours, confirming that hormone determinations occurred early during the course of disease. In that same study, foals with negative blood culture and sepsis score55 less than or equal to 10 hospitalized for conditions other than sepsis, for example, neonatal isoerythrolysis or neonatal encephalopathy (also known as perinatal asphyxia syndrome and dummy foal), also had elevations in HPAA hormones, to a lesser magnitude, however, than septic foals. AVP concentration was also found significantly associated with survival; foals with high AVP concentrations were more likely to die.28
Systemic hypotension is reported commonly in septic foals\textsuperscript{49,56–59} and is also associated with increased AVP concentration in the acute stage of sepsis in humans.\textsuperscript{34} In a study by Hurcombe and colleagues,\textsuperscript{28} a normal calculated serum osmolality was found in foals with high AVP concentrations, suggesting that nonosmotic stimuli were responsible for AVP release (ie, hypotension or hypoperfusion [baroreceptor-mediated release] and systemic inflammation [stress-mediated release]). In further assessment of HP axis activation in septic foals, ACTH concentrations were measured in conjunction with AVP. Septic foals and sick nonseptic foals had proportionally higher plasma ACTH concentrations compared with healthy foals. Median plasma ACTH concentrations were significantly higher in septic than in sick nonseptic foals, which, in turn, were significantly higher than in healthy foals. In addition to CRH,\textsuperscript{10,60} AVP is a major pituitary ACTH secretagogue,\textsuperscript{7–11} which may explain why foals with increased AVP also had increases in ACTH, as seen in a previous study in foals.\textsuperscript{61}

Again, proposed mechanisms for increased ACTH concentrations are likely similar to those described for increased AVP release. Other mechanisms may include RAI or CIRCI, where adrenocortical exhaustion and lack of cortisol production provide a positive stimulus for ACTH release in times of extreme stress. This phenomena has been described in critically ill people\textsuperscript{34,62–64} and more recently in septic foals.\textsuperscript{29,30} RAI is diagnosed in foals by a decreased baseline cortisol concentration and/or subnormal response in cortisol release after administration of low- and/or high-dose exogenous ACTH\textsuperscript{29,65} (see article elsewhere in this issue by Hart and Barton). In human critical care, an increase in cortisol by at least 9 $\mu$g/dL is useful to rule out RAI (delta-9 rule); however, this cutoff is both controversial and species specific.

These results are consistent with limited published data in septic foals\textsuperscript{27} but differ from some results of sepsis studies in humans, where ACTH and cortisol concentrations often were low. Differences may be explained by species variation, age of subject, duration of illness, and severity of illness.\textsuperscript{62–64}

The utility of determining hormone ratios can also provide a rough estimation of function. This is not a substitute but a surrogate for more accurate measure of assessing HPAA function, such as cosyntropin (exogenous ACTH) stimulation testing.

AVP:ACTH and ACTH:cortisol ratios were determined and significantly higher in septic foals compared with sick nonseptic foals and healthy foals in two studies.\textsuperscript{27,28} In those critically ill foals where a marked increase in AVP and concomitant normal or low ACTH concentration were found, this finding would be supportive of pituitary dysregulation or relative pituitary insufficiency. CRH:ACTH ratios may also indicate dysfunction at the level of the pituitary gland. To test this theory, a CRH stimulation test might be useful to determine appropriate pituitary responsiveness.

An increase in AVP and ACTH may indicate an appropriate HPAA response to critical illness. Despite increases in these hormones, affected foals were likely to have systemic perfusion impairment. This observation may indicate an inappropriate target organ response, such as adrenocortical unresponsiveness or exhaustion (CIRCI), or inappropriate vascular endothelium responsiveness, where physiologic increases in AVP concentration were insufficient to mediate vasoconstriction, through unknown mechanisms. One could postulate that potential V\textsubscript{1} receptor refractoriness or exhaustion was a possible cause. Increases in AVP and ACTH were in agreement with previous studies assessing HPAA maturity in newborn foals\textsuperscript{6} and suggest that HPAA stimulation occurs as a result of acute critical illness in young foals and that the magnitude of stimulation is proportional to the severity of disease and outcome and not necessarily changes in serum osmolality.\textsuperscript{28} In light of these findings, further evaluation of hormone dynamics over time would be required to assess if AVP...
depletion or relative vasopressin deficiency occurs in septic foals, as has been described in people; however, this information is currently lacking.

To date, much of the available information regarding endocrinopathies of critical illness center on the adrenal as the target organ; however, HPA dysfunction likely occurs at multiple levels and further identification and definition of these abnormalities may yield therapeutic targets.

Colic (Abdominal Pain)

Acute abdominal pain represents a major stress to activate the HPAA in horses. Blood cortisol and catecholamine concentrations have been associated with survival in horses with colic. The mean cortisol concentration was 7.1 μg/dL in survivors and 15.4 μg/dL in nonsurvivors, and nonsurvivors were 1.28 times more likely to die than survivors (crude, unadjusted odds ratio; \( P = .037 \)).\(^6\) These results are consistent with a more recent study evaluating baseline (admission) β-END, heat shock protein 72, cortisol, and ACTH concentrations in horses with colic. β-END, ACTH, and cortisol were related to the severity of colic and likelihood of survival.\(^6\) More recently, Ludders and colleagues\(^5\) showed that horses with colic had an 8-fold preanesthesia AVP elevation than horses with elective arthroscopy, and AVP concentrations remained elevated longer during anesthesia (\( P < .001 \)).

Hypothalamic-Pituitary Dysfunction, Stress, and the Performance Horse

Stress has been defined as any event that results in increased activity of the HPAA and a subsequent increase in plasma corticosteroid concentrations.\(^6\) In times of stress, stimulation of the HPAA to yield an increase in cortisol has several life-preserving functions, including permissive effects on intermediary metabolism, such as catecholamine-mediated lipolysis and free fatty acid synthesis. Glucocorticoids also promote energy production through glycolysis, lipolysis, and protein catabolism. Another important action of cortisol is to enhance the vascular responsiveness to endogenous catecholamines, which facilitates vascular integrity and blood flow to vital organs during stress.\(^1,14\)

A neuroendocrine disorder at the level of the HP axis has been suggested as the cause of the overtraining syndrome, defined as a homeostatic disturbance at the cellular level resulting in longer recovery post-training times in horses. Clinical findings in these horses include poor performance, poor appetite, weight loss, mental instability/irritability, lack of competitive drive, reproductive cycling abnormalities, increased susceptibility to illness, and persistent tachycardia after exercise, to name a few.\(^6\) Chronic stress in horses has also been found to result in poor fractional change in pituitary venous concentrations of ACTH after administration of human CRH (2 μg). Of importance, there is 100% amino acid homology between human and equine CRH,\(^1\) which has clinical value for testing the pituitary and adrenal components of the axis. Similarly, Alexander and Irvine looked at social stress and found that horses showed decreased in corticosteroid-binding globulin) concentrations, resulting in increased free cortisol concentrations in plasma.\(^7\)

The stress endocrine response to transport has also been evaluated in horses submitted to different lengths of transportation. One study measured β-END, ACTH, and cortisol responses in healthy stallions transported 300 km with jugular venous blood sampling every 100 km. Increases in all 3 hormones were observed with cortisol concentrations remaining elevated over the entire distance, indicating persistent activation and/or a longer half life.\(^7\) The HPAA responses to transportation can result in altered pulmonary macrophage function, which is permissive for the development of (pleuro)pneumonia.
VASOPRESSIN AND THE KIDNEY

Relative and absolute AVP deficiency can result in DI. The hallmark feature of this uncommon condition of horses is polyuria without loss of water in the urine. This alone should be a potent stimulus for AVP release; however, either the target organ is unresponsive to the circulating AVP (nephrogenic DI) or no AVP is released in response to hyperosmolality (central or pituitary-dependent DI). Nephrogenic DI results from a lack of AVP signaling in the collecting ducts to assemble and mobilize aquaporin-2 channels and reclaim water despite adequate AVP response stimulation (eg, hypertonicity, hypovolemia). Central DI results from a lack of synthesis and release of AVP. Without AVP, water reabsorption does not occur, resulting in voiding of large volumes of hyposthenuric urine. In both forms, the ability of the nephron to concentrate tubular fluid is lacking. Horses with central DI should respond to exogenous AVP administration (water reabsorption) by increasing their urine-specific gravity (adequately >1.015) and osmolality and decreasing their urine volume and serum osmolality. A thorough review of DI can be found elsewhere in this issue in the article by Schott.

Finally, another disorder of AVP control is the SIADH, where there is an inappropriate release of AVP. This can be due to structural central nervous system disease or drugs or can be idiopathic. SIADH is recognized in humans and dogs and characterized by hyponatremia, increased urine osmolality, and possible circulatory overload, although most patients are euvoletic. Currently, this has not been reported in horses but may be possible.

HYPOTHALAMIC-PITUITARY DYSFUNCTION AND DOPAMINE

As discussed previously, dopamine is an inhibitory neurotransmitter to several cell types of the pars distalis and pars intermedia. Increased dopaminergic input to the pituitary gland results in a reduction in the synthesis and secretion of prolactin, GH, TSH, and POMC peptides. A decrease in dopaminergic input to the pituitary pars intermedia can result in melanotroph hyperplasia and is the pathogenic basis for the development of equine PPID. Under the premise that dopamine is an inhibitory factor for melanotroph function, dopamine agonists are used to treat PPID (see the article by MacFarlane elsewhere in this issue).

Exogenous dopaminergic alkaloids can lead to reproductive and perinatal abnormalities in the mare and foal. Tall fescue (Festuca arundinacea) infested with the endophyte, Neotyphodium coenophialum, has toxic amounts of dopaminergic ergopeptine alkaloids (derivatives of lysergic acid). This dopaminergic dominance over the pituitary gland inhibits prolactin secretion, causing agalactia and poor/absent mammary gland development. Many other manifestations, including thickened placenta, abortion, prolonged gestation, dystocia, and weak or dead foals can occur in late-term pregnant mares. Foals born to mares exposed to Neotyphodium-infested fescue have altered HPA and HPT axis dysfunction, where ACTH, thyroxine, triiodothyronine, progestagen, and cortisol concentrations are lower than healthy foals. These fetal endocrine abnormalities are associated with prolonged gestation. For detailed information on dopaminergic alkaloids, see the article by Evans elsewhere in this issue.

Exogenous DA receptor antagonists (domperidone and metoclopramine [DA2 receptor antagonists], sulphiride [DA2 and DA3 receptor antagonist], and phenothiazines [DA receptor antagonists]) can reverse the inhibitory effects of DA, increasing prolactin secretion. Removal of pregnant mares from infested pastures by day 300 of gestation results in a rapid decline in alkaloid exposure, increasing progestagen
and prolactin concentrations. Thus, mares should be off tall fescue pastures 30 to 60 days before the expected foaling date.

SUMMARY

The HP axis (and HPAA) is a tightly regulated endocrine feedback and feed-forward system essential to cellular and organ function as well as physiologic adaptation in horses. Although an understanding of the normal responses to stress is fairly well understood, the responses to critical illness are limited. The body of evidence that HP axis dysfunction in the horse truly exists is mounting. Further investigation as to complete endocrine dynamics in response to critical illness (eg, endotoxemia/sepsis, SIRS, multiple-organ dysfunction syndrome, and trauma), methods to diagnose HP dysfunction, and specific therapies (eg, fluid therapy, antiendotoxic therapies, anti-inflammatory drugs, and hormone replacement therapy) is ongoing. Specifically, the rationale for glucocorticoid administration in septic patients with CIRCI/RAI is evident. The benefit, however, is yet to be determined. This important adaptive axis deserves more attention and investigation because therapies targeting different levels of the HPAA may yield favorable outcomes and increase survival in critically ill horses/foals, as seen in other species.

REFERENCES


