Review of Current Understanding of Pituitary Pars Intermedia Dysfunction

Dianne McFarlane, DVM, PhD, Diplomate ACVIM

Equine pituitary pars intermedia dysfunction (PPID) is a commonly diagnosed disease in the aged equine population. Recognition of PPID has increased considerably over the past two decades, in part because of an increase in client awareness of the condition as well as an increase in the number of aged horses receiving veterinary equine PPID care. This review focuses on the most current understanding of the development and progression of equine PPID. Author's address: Oklahoma State University, Department of Physiological Sciences, Center of Veterinary Health Sciences, Stillwater, OK 74078; e-mail: diannem@okstate.edu.

1. Introduction

Anatomy and Function of the Equine Pituitary

The equine pituitary gland lies ventral to the optic chiasm, separated from the brain by a fold of dura mater known as the diaphragma sellae. It is suspended from the hypothalamus by the infundibular stalk. The equine pituitary gland has four lobes; the pars distalis, pars intermedia, pars tuberalis (collectively known as the adenohypophysis), and pars nervosa (neurohypophysis).

Melanotropes of the pars intermedia produce a hormone precursor protein, pro-opiomelancortin (POMC), which undergoes extensive tissue-specific cleavage to yield adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormones (MSH), β-endorphin, corticotrophin-like intermediate lope peptide (CLIP), lipotropins, and several other small peptides. In the pars intermedia of the healthy animal, the primary hormones produced are α-MSH, β-endorphin, and CLIP. Nearly all plasma ACTH originates from the pars distalis, and minimal ACTH is produced in the pars intermedia of the healthy horse.[1]

Equine pars intermedia activity has been shown to be inhibited by dopamine and stimulated by thyrotopin-releasing hormone.[2,3] The pars intermedia receives direct innervation from the dopaminergic neurons of the periventricular nucleus of the hypothalamus. These axons project through the infundibular stalk along the periphery of the pars nervosa, then travel into the pars intermedia, where they terminate on the endocrine cells of the pars intermedia, the melanotropes. Dopamine is released at the pars intermedia from the nerve terminals of the hypothalamic periventricular neurons that synapse directly on the melanotropes.[4] In the presence of dopamine secretion of pars intermedia, POMC-derived peptide hormones are decreased. If dopamine is removed either by surgically cutting the hypothalamic pituitary connection or by genetically deleting the dopamine receptor, melanotropes will proliferate, hypertrophy, and increase production of POMC-derived peptides.[5–7]

NOTES

The products of POMC are diverse and highly pleiotrophic in function. α-MSH has a role in metabolism, obesity, stress, and inflammation. Because of these critical functions, this hormone is currently the focus of significant research attention, with more than 1250 PubMed citations in the past 5 years alone. α-MSH induces an anorexic response and feeling of satiety[8] and has broad anti-inflammatory effects that include decreased production of a wide array of cytokines and other molecules, factors that contribute to inflammation.[9,10] α-MSH also impairs neutrophil function, including oxidative burst, chemotaxis, and adhesion.[11,12] CLIP is the cleavage product generated from the c-terminal portion of ACTH. Little is known about the function of CLIP; however, both CLIP and its cleavage product, β-cell tropin, have been shown to stimulate the release of insulin from rodent beta cells.[13] β-Endorphin is a potent endogenous opioid μ-receptor agonist that functions in analgesia and reduction of pain-associated inflammation.

Similar to several other species such as hamsters and sheep, activity of the pars intermedia in horses has a robust seasonal rhythm, with increased output occurring as day length shortens.[14–19] As a result, the plasma concentration of the pars intermedia hormones, including α-MSH, are greater in the autumn (August through October) than in the winter or spring.[18,19] It has been suggested that this adaptation helps to prepare the animal for the metabolic and nutritional pressures of the approaching winter.

2. Pituitary Pars Intermedia Dysfunction

Equine PPID is associated with increased size and activity of the pars intermedia. At necropsy, horses with PPID have enlarged pituitary glands caused by hyperplasia, hypertrophy, and a single large or multiple small adenomas. Enlargement of the pars intermedia is often accompanied by compression of adjacent structures. PPID was previously characterized as a benign neoplasia of the equine pituitary gland; however, clinical, pharmacological, biochemical, and histological data all indicate that PPID is a neurodegenerative disease with loss of inhibitory dopaminergic input to the pars intermedia. Typical of any neurodegenerative disease, age is the primary risk factor for PPID, and progression of clinical signs occur slowly, making early diagnosis problematic.

In horses with PPID, there is a marked reduction of dopamine in pars intermedia tissue[20] as well as a profound loss of dopaminergic periventricular nerve terminals and cell bodies.[21] Further evidence that PPID results from loss of dopamine is the improvement in clinical signs and plasma hormone concentration that is observed when horses with PPID are treated with a dopamine agonist such as pergolide.[22–24] Although the precise cause of neurodegeneration in PPID is unknown, several studies have provided evidence that oxidative damage occurs to the dopaminergic neurons, although at this time it is unknown whether oxidative stress is a cause or consequence of PPID.[25–27]

Neuronal accumulation and aggregation of misfolded proteins is a mechanism that contributes to the pathogenesis of most neurodegenerative diseases, including Parkinson's disease, a dopaminergic neurodegenerative disease of aged people. In Parkinson disease, the protein that accumulates in the dopaminergic neurons is α-synuclein. α-Synuclein is natively unfolded; however, under certain cellular conditions, α-synuclein can aggregate in dopaminergic nerve terminals, disrupting cellular function and triggering cell death.[28] Conditions that promote accumulation of α-synuclein include excessive concentration caused by increased production or decreased clearance, oxidation or nitration, and synuclein gene mutations.[29,30] α-Synuclein protein and gene expression was found to be increased in the pars intermedia of horses with PPID.[21] In addition to being more abundant, pars intermedia α-synuclein appears to be excessively nitrated in horses with PPID, a modification that promotes aggregation.[21] It is unknown if failure of protein clearance also contributes to α-synuclein accumulation in horses with PPID. Misfolded proteins are removed primarily through autophagy, the process by which damaged proteins or organelles are recycled by the lysosome.[31] Assessment of autophagy in the periventricular neurons of horses with PPID is ongoing.

3. Clinical Signs of PPID and Diagnostic Testing

Clinical signs of PPID probably are the result of overexpression of the pars intermedia hormones. Late in the disease, it is also possible that loss of hormones from the adjacent, compressed lobes of the pituitary may also contribute to the clinical syndrome. Weight loss caused by muscle atrophy, behavioral changes, secondary infections, and changes in haircoat are some of the most common signs of PPID. Laminitis occurs with PPID but less frequently than was originally suggested. It is likely that laminitis occurs only in horses with PPID and concurrent insulin dysregulation. Further work is ongoing to identify the mechanism of development of endocrinopathic lamintis.

Testing for PPID involves measurement of endogenous hormone concentrations, including ACTH or α-MSH or dynamic testing. Dynamic testing, which measures the response of the pars intermedia to stimulation or inhibition, may be a more discriminating approach to disease diagnosis. Because of the increase in PI activity in the fall, false-positive diagnostic test results for PPID are common when testing is performed during the autumn if reference intervals are not adjusted for season.[18–20] In addition, clinical signs of PPID are often more pronounced in the autumn, most notably an increased incidence of laminitis.[32] Because pasture composition also changes significantly with season,

studies are needed to determine the role of hormone increase in seasonal development of laminitis.[33] Diagnostic testing for PPID will be discussed in more detail in another session.

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