Corticosteroids and Immune Suppressive Therapies in Horses

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KEYWORDS

• Azathioprine • Equine asthma • Glucocorticoids • Glucocorticosteroids
• Immune-mediated • Immunomodulation

KEY POINTS

- Glucocorticoids are the most commonly used immune suppressive drugs and the only class supported by robust evidence of clinical efficacy in equine medicine.
- Other immune suppressive agents used in horses include azathioprine, cyclophosphamide, and cyclosporine.
- Strategies to decrease side effects of glucocorticoids include using local and combination therapy.

INTRODUCTION

Immune suppressive therapies target exaggerated and deleterious responses of the immune system. These immune responses can lead to several clinical manifestations in horses, including atopy and skin hypersensitivity reactions, equine asthma, pemphigus, vasculitis (including purpura hemorrhagica), eosinophilic granuloma, mastocytosis, inflammatory bowel syndrome, recurrent uveitis, and immune-mediated keratitis, anemia, thrombocytopenia, and myositis. Glucocorticoids are the most commonly used immune suppressive drugs and the only ones supported by robust evidence of efficacy in equine medicine. Their efficacy has been demonstrated and compared with other drugs primarily in the context of research on equine asthma. The paucity of available data on immunosuppressive therapy in horses is due in part to the complexity of the immune system as well as the chronic and recurrent manifestations of the many diseases targeted with immune suppressive therapy. Other immune suppressive agents used in horses include azathioprine, cyclophosphamide, and local cyclosporine. Alternative therapies without clearly demonstrated immunosuppressive effects (eg, acupuncture, herbal medicine) are not covered in this review.

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GLUCOCORTICOIDS (CORTICOSTEROIDS)

Glucocorticoids, also called corticosteroids, are the most effective anti-inflammatory and immunosuppressive drugs available for the treatment of many chronic inflammatory and immune diseases across species. The hypothalamus releases corticotropin-releasing hormone into the portal system of the pituitary gland, which in turn releases adrenocorticotropic hormone (ACTH). This ACTH induces cortisol synthesis and release by the adrenal cortex into the bloodstream. Cortisol then targets glucocorticoid receptors present in almost every cell of the body.[1,2] Synthetic corticosteroids have a similar 21-carbon steroid skeleton, with the addition of a C1-C2 double bond, and bind to the same glucocorticoid receptor as cortisol. Glucocorticoids will only be discussed in the context of immune suppressive therapy, but some glucocorticoids used in equine medicine also have an affinity for mineralocorticoid receptors (eg, prednisolone, isoflupredone).

Glucocorticoids exert most of their anti-inflammatory and immunosuppressive effects by diffusing across the cell membrane and binding the glucocorticoid receptors in the cytoplasm.[3] After releasing the receptor chaperon proteins, glucocorticoids and their receptors translocate into the cell nucleus and alter gene expression (illustrated in Fig. 1). Anti-inflammatory effects generally result from gene transrepression leading to transcription factor repression (such as NF-κB and AP-1) and downregulation of inflammatory chemokines and cytokines (eg, interleukin-1 [IL-1], IL-6, tumor necrosis factor) as well as adhesion molecules. Glucocorticoids also result in gene transactivation following direct DNA binding, which increases the release of anti-inflammatory mediators, but also leads to undesirable metabolic effects.

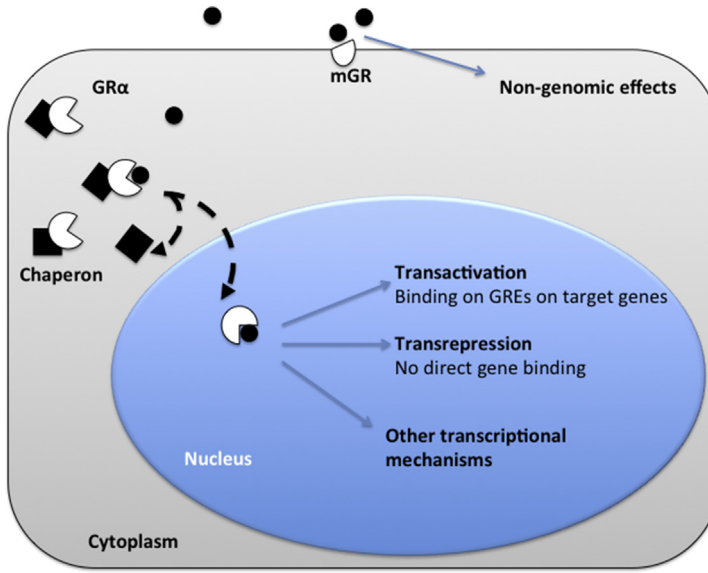

Fig. 1. Glucocorticoids (*black circles*) binding to the major receptor, the cytoplasmic glucocorticoid receptor isoform α (GRα, *white*), and displacing chaperon proteins (such as heat shock proteins; *black squares*) before entering the nucleus. mGR, membrane-associated glucocorticoid receptor. GREs, glucocorticoid response elements. (*Data from* Hall JE. Adrenocortical hormones. Guyton and Hall textbook of medical physiology. 13th edition. Philadelphia: Elsevier Health Sciences; 2015. p. 965–82; and Hapgood JP, Avenant C, Moliki JM. Glucocorticoid-independent modulation of GR activity: implications for immunotherapy. Pharmacol Ther 2016;165:93–113.)