

# The Pharmacologic Basis for the Treatment of Endocrinopathic Laminitis

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## KEYWORDS

- Laminitis • Endocrine • Cushing's disease • PPID
- Metabolic syndrome • Treatment

The causal factors and pathophysiology of equine laminitis have been the subject of much research in the last 40 years. Evidence of possible endocrine involvement in the development of laminitis was first raised by an *in vitro* study by Eyre and colleagues<sup>1</sup> in 1979 who found that digital vasoconstriction induced by epinephrine, norepinephrine, and serotonin was potentiated in the presence of glucocorticoids. Subsequently, a few anecdotal reports describing laminitis following glucocorticoid therapy were published creating a contentious debate regarding the perceived risks of glucocorticoid use in equine practice.<sup>2</sup> During the 1980s, an association between laminitis and insulin resistance (IR) was first demonstrated<sup>3–5</sup> and this association has enjoyed a recent surge in interest following the review by Johnson<sup>6</sup> in 2002 in which the equine metabolic syndrome (EMS) was first proposed to explain the clustering of obesity, IR, and laminitis in certain individuals. In the meantime the complex age-related endocrinopathy associated with pituitary pars intermedia dysfunction (PPID, equine Cushing's disease) has become increasingly recognized by equine practitioners presented with ageing horses suffering from laminitis.<sup>7</sup> Other endocrine disturbances have been described in horses with laminitis including low concentrations of thyroid hormones and increased concentrations of testosterone, catecholamines, rennin, and aldosterone although any causal association between these findings and laminitis is considered unlikely.<sup>8,9</sup> Thus endocrinopathic laminitis, whereby endocrine disturbances cause or predispose to the development of laminitis, is regarded as comprising iatrogenic glucocorticoid-induced laminitis, PPID, and EMS.

Although the treatment and management of laminitis in the horse requires a holistic and often multidisciplinary approach from the veterinarian, farrier, and nutritionist, this

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review focuses on pharmacologic interventions that might have prophylactic benefit, specifically in the horse with laminitis as a result of PPID and EMS.

## PHARMACOLOGIC TREATMENT OF PPID

Laminitis is a prominent clinical feature of PPID with a combined prevalence of 56% of 223 PPID cases described in 7 recent studies.<sup>7,10–15</sup> Despite this, the pathophysiology of laminitis in PPID is not well understood and might involve endogenous glucocorticoid effects, IR, hyperinsulinemia, and/or other mechanisms. However, hypercortisolemia is not a consistent finding in PPID cases<sup>16,17</sup> and not all horses with PPID have IR or hyperinsulinemia.<sup>18</sup>

### *Dopamine Agonists*

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The fundamental pathophysiologic process that leads to development of PPID is believed to be oxidative damage to hypothalamic dopaminergic neurones that normally exert a tonic inhibitory influence on the melanotrophs of the pars intermedia of the anterior pituitary gland.<sup>19</sup> Reimposition of dopaminergic inhibition via exogenously administered dopamine agonists is a logical and attractive pharmacologic strategy, and has been shown experimentally to reduce secretion from the pars intermedia in the horse.<sup>20</sup> Pergolide mesylate, a combined D1/D2 dopamine receptor agonist, has become the first-line treatment of PPID in horses.<sup>21–23</sup> However, no pharmacokinetic data for pergolide in the horse have been published. In humans the drug is absorbed rapidly and has a long half-life leading to a relatively stable and physiologic plasma concentration profile.<sup>24</sup> Evidence of a rapid onset of effect has also been demonstrated in horses<sup>25,26</sup> and single daily dosing seems clinically efficacious.<sup>21–23</sup> In the past, pergolide was often administered to horses at doses as high as 0.010 mg/kg by mouth once a day<sup>27</sup> although following a 1995 report describing good efficacy of lower doses,<sup>28</sup> it is now widely accepted that between 0.001 and 0.003 mg/kg by mouth once a day is more appropriate.<sup>22,23</sup> The commonest adverse effect of pergolide therapy in horses is anorexia typically affecting 5% to 10% of treated cases, although colic and diarrhea are also reported rarely.<sup>22,23</sup> The problem of inappetance can usually be overcome by stopping treatment for a few days and then recommencing at a lower dose.<sup>23</sup> Although once prescribed for the treatment of Parkinson disease and Cushing's disease in humans, pergolide was withdrawn in the United States as a human medicine in 2007 because of concerns of increased risk of pulmonary and cardiac valvular fibrosis.<sup>29</sup> Compounding pharmacies continue to supply pergolide for veterinary species within the United States although, in Europe, any future withdrawal of pergolide as a human-licensed medicine could create problems for its continued equine use. Bromocryptine mesylate, another dopamine agonist, has also been reported as an effective treatment of PPID in horses at a dose of 0.005 to 0.03 mg/kg intramuscularly twice a day or 0.03 to 0.09 mg/kg by mouth twice a day<sup>30</sup> although this drug has not proved to be popular in equine practice. There are many other dopamine agonists used in human medicine that might be investigated in horses should the need arise.<sup>31,32</sup>

### *Cyproheptadine*

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Cyproheptadine hydrochloride, a serotonin, acetylcholine, and histamine antagonist has also been advocated for treatment of PPID in horses. The drug has been found to reduce corticotrophin secretion from corticotrophs in the pars distalis of humans via direct and antiserotonergic mechanisms and to have clinical benefits in some cases of human Cushing's disease.<sup>33,34</sup> However, the same effects have not been

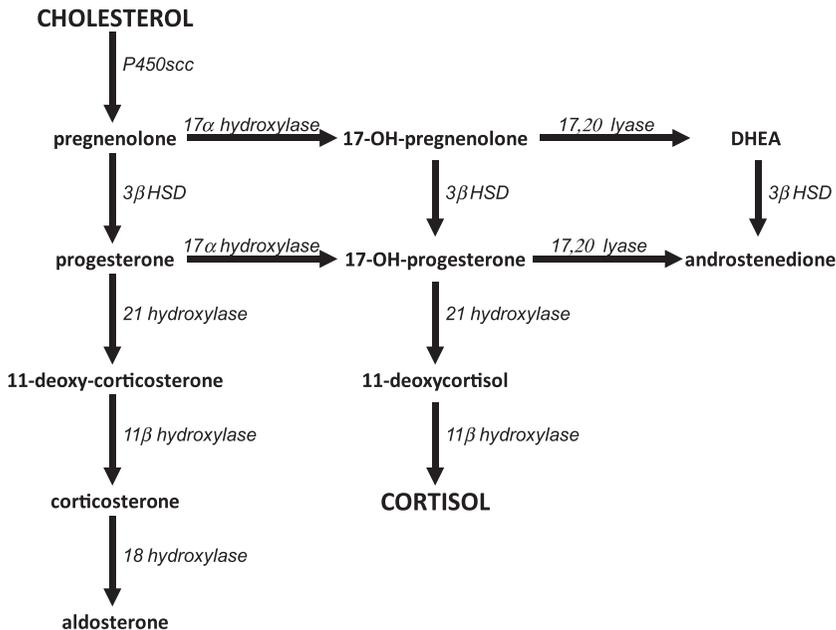
investigated in dysfunctional melanotrophs of the pars intermedia in horses with PPID. Nevertheless clinical and endocrine benefits of cyproheptadine therapy are described in horses receiving doses of 0.25 mg/kg by mouth once or twice a day.<sup>35</sup>

### ***Inhibitors of Cortisol Synthesis***

Despite the popularity and efficacy of pergolide and cyproheptadine in equine medicine, a similar pharmacologic strategy in human cases of Cushing's disease is generally of limited benefit.<sup>36</sup> Attempts to moderate adrenal biosynthesis of glucocorticoids is the favored medical approach in humans using the enzyme inhibitors ketoconazole, aminoglutethimide, metyrapone, and the enzyme inhibitor/adrenolytic agent mitotane (**Fig. 1, Table 1**).<sup>36</sup> The use of these agents in the horse has not been properly studied although mitotane is described as ineffective in a few anecdotal reports.<sup>22</sup> This author has used aminoglutethimide and metyrapone, at a dose of 2 to 4 mg/kg by mouth once a day, in several cases in the last 15 years with a generally favorable clinical impression and evidence of improvement in clinicopathologic tests in some cases. Trilostane, a  $3\beta$ -hydroxysteroid dehydrogenase inhibitor, is not favored in human patients<sup>37</sup> but has been used successfully in pituitary-dependent hyperadrenocorticism in dogs<sup>38</sup> and is the only drug in this class subject to published investigation in horses. Trilostane was shown to inhibit the conversion of pregnenolone to progesterone after intravenous infusion in horses<sup>39</sup> and was subsequently investigated in PPID cases. A good clinical response was observed after 30 days of treatment with trilostane at 0.5 to 1.5 mg/kg by mouth once a day along with some improvement in endocrine tests in a study of 20 PPID cases although a control group was not compared.<sup>40,41</sup>

### ***Drug Selection in PPID***

A few comparative studies of the relative benefits of treatments for equine PPID cases have been published. These have generally found pergolide to be more efficacious



**Fig. 1.** Adrenal corticosteroid biosynthesis (P450scc, side chain cleavage enzyme;  $3\beta$ HSD,  $3\beta$ -hydroxysteroid dehydrogenase). See **Table 1** for enzymes targeted by therapeutic products.

**Table 1**

**Enzyme targets of adrenal corticosteroid biosynthesis inhibitors (only trilostane has been the subject of a published study in the horse). See Fig. 1 for enzymatic actions (P450scc, side chain cleavage enzyme; 3 $\beta$ HSD, 3 $\beta$ -hydroxysteroid dehydrogenase)**

	P450scc	17 $\alpha$ -Hydroxylase	3 $\beta$ HSD	17,20-Lyase	11 $\beta$ -Hydroxylase
Aminoglutethimide	×				
Ketoconazole	×	×		×	
Metyrapone					×
Mitotane	×				×
Trilostane			×		

than cyproheptadine<sup>12,13,27</sup> although similar efficacy of the 2 drugs was shown by 1 study.<sup>14</sup> Comparison of the benefits of the herbal remedy *Vitex agnus castus* versus pergolide in 12 horses found no benefit of the former product but a good response to pergolide therapy in most cases.<sup>42</sup> Given the differing modes of action of many of the drugs used for PPID, there may be justification to consider drug combinations in poorly responsive cases and anecdotal reports exist describing the benefits of this approach.<sup>22</sup>

Cost of treatment is an important consideration in drug selection. Comparison of current costs in the United Kingdom reveal a standard dose of cyproheptadine (0.25 mg/kg twice a day) to be approximately 6 times the cost of pergolide (0.002 mg/kg once a day); and a standard dose of trilostane (1 mg/kg once a day) to be almost 20 times the cost of pergolide. The relative cost of these 3 drugs is similar in the United States depending on the source of pergolide (branded vs compounded). When this is considered alongside an appraisal of the published evidence outlined earlier then pergolide seems to be the unequivocal recommendation for first-line treatment of PPID in horses.

## PHARMACOLOGIC TREATMENT OF EMS

Quantification of the risk of developing laminitis in horses with EMS is confounded by the inclusion of history of previous laminitis as part of the EMS definition.<sup>43</sup> In a recent prospective study, it was found that 11/55 (20.0%) individuals with the characteristics of EMS developed laminitis compared with 2/82 (2.4%) in a control group, although previous history of laminitis and familial associations may have biased this finding.<sup>44</sup> No prospective studies have yet been published that examine the incidence of de novo laminitis in obese and insulin-resistant subjects.

Most studies in humans have shown lifestyle modification, including diet, exercise, and smoking, to have the greatest beneficial effects on the metabolic syndrome and associated disease risk.<sup>45</sup> However, improvements are hard to sustain and reversion to previous lifestyle risks is frequent. In equid subjects, one might expect management changes to be more easily adhered to by a motivated owner although inability to exercise chronically lame individuals and resistance to diet-induced weight loss in easy-keeper types still present challenges. The importance of diet and exercise management of EMS cases cannot be overemphasized,<sup>43,46</sup> but nevertheless interest has arisen in pharmacologic therapies that might reduce laminitis risk by moderating components of the EMS.

Knowledge and understanding of the metabolic syndrome in humans is far more advanced than the analogous equine condition. There are multiple potential therapeutic aims for pharmacologic interventions in humans including management of

obesity, IR, hyperinsulinemia, hyperglycemia, dyslipidemia, systemic inflammation, hypertension, and procoagulant status. Not all of these factors have been shown to be present and/or pathophysiologically relevant in EMS cases and therefore therapeutic ambitions of equine clinicians are currently unlikely to extend beyond the possible moderation of obesity, IR, hyperinsulinemia, and hyperglycemia (if present). Evidence supporting the pathophysiologic importance of obesity, IR, and hyperinsulinemia in laminitis risk has been published previously.<sup>44,47,48</sup> Hyperglycemia is an uncommon finding in EMS cases although statistical comparison with blood glucose in normal individuals has not been fully investigated. Even mild increases in blood glucose have been shown to promote endothelial dysfunction, inflammation, and coagulation in humans,<sup>49</sup> and therefore antihyperglycemic therapy might still be beneficial even in equine subjects with blood glucose within (upper) reference intervals.

### ***L-Thyroxine***

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Currently the only pharmacologic treatment of horses with EMS that has a good evidence basis is L-thyroxine (eg, Thyro L, Lloyd Inc, Shenandoah, IA; Soloxine, Virbac Ltd, Bury St Edmunds, Suffolk, UK). In one study, daily administration of 0.1 mg/kg L-thyroxine was found to double the baseline insulin sensitivity of euthyroid horses following 16, 32, and 48 weeks of treatment.<sup>50</sup> The mechanism underlying the beneficial effect of L-thyroxine on insulin sensitivity is currently unclear and might involve direct effects on insulin-glucose metabolism and/or an indirect effect via induced weight loss.<sup>50</sup> L-Thyroxine treatment as described earlier has not been associated with significant adverse effects<sup>51</sup> although its use in nonobese insulin-resistant horses is questionable without further study. Current recommendations are to treat obese EMS cases with L-thyroxine at a dose of 0.1 mg/kg by mouth once a day for between 3 and 6 months during which time strict dietary control is essential. When satisfactory bodily condition has been achieved then L-thyroxine should be gradually withdrawn by administering a half dose for 2 weeks followed by a quarter dose for a further 2 weeks (Nicholas Frank DVM, PhD, DACVIM, Knoxville, TN, personal communication, November 2009).

### ***Lessons from Human Metabolic Syndrome?***

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Based on efficacy, cost, and availability, the mainstays for medical management of the metabolic syndrome in humans are the biguanide metformin and the sulfonylurea glyburide (glibenclamide).<sup>52,53</sup> The other main therapeutic choices are listed in **Table 2**.<sup>52–55</sup> More than 50 natural products have also been suggested as having beneficial actions in insulin-resistant humans and horses but currently lack any strong evidence basis.<sup>54,56,57</sup> However, considerable caution should be exercised in the extrapolation of findings from human to equine studies as it is apparent that many significant differences exist between the 2 species in terms of pharmacokinetics and the pathophysiology of the metabolic syndrome in humans versus horses. Appetite suppressants have proved useful in the management of the metabolic syndrome in human patients but could well be hazardous in EMS because of the significant risks of inducing hyperlipemia in hypophagic insulin-resistant subjects. Inhibitors of carbohydrate digestion have been used to good effect in humans although the likely increased cecal carbohydrate delivery may actually increase laminitis risk in horses. Insulin secretagogues are commonly used in people who have lost effective compensatory pancreatic insulin secretion in response to chronic IR. Such cases would seem to be relatively uncommon in horses although glyburide (glibenclamide), the most commonly prescribed secretagogue in human subjects, has been administered to horses with type 2 diabetes mellitus.<sup>25,58</sup> Further concerns with the use of insulin

<b>Drug Class</b>	<b>Examples</b>	<b>Main Mode of Action</b>
Biguanides	Metformin	Insulin-sensitization (hepatic)
Thiazolidinediones	Pioglitazone, Rosiglitazone	Insulin-sensitization
Sulfonylureas	Glyburide/Glibenclamide	Increased insulin secretion
Glinides	Repaglinide, nateglinide	Increased insulin secretion
Insulin and analogues	Insulin, insulin detemir	Compensation for reduced insulin secretion
$\alpha$ -Glucosidase inhibitors	Acarbose	Inhibition of carbohydrate digestion
Amylin analogues	Pramlintide	Glucagon suppression, appetite suppression
Incretin mimetics	Exenatide	Increased insulin secretion, $\beta$ -cell regeneration, glucagon suppression, appetite suppression
Dipeptidyl peptidase IV antagonists	Sidagliptin, vildagliptin	Prolongation of glucagonlike peptide-1 (incretin) activity (see row above)

secretagogues and exogenous insulin therapy include the potential for inducing hypoglycemia and weight gain as well as the potentially adverse consequences of stimulating higher circulating insulin concentrations that could increase laminitis risk.<sup>47,48,52,53,59,60</sup>

Consideration of the pharmacologic properties of the various drugs used in the treatment of the metabolic syndrome in human patients has stimulated particular interest amongst equine clinicians in the insulin-sensitizing drugs, metformin and the thiazolidinediones. Although these drugs might seem logical choices for the treatment of IR in humans and horses, it is evident that they have multiple actions, not all of which are beneficial, and that adverse reactions are a serious consideration with novel deployment of any therapeutic product.

### **Metformin**

Metformin, a biguanide, is a synthetic analogue of guanidine found naturally in the plant *Galega officinalis*. Metformin has been used for almost 50 years in Europe in human patients but was only made available in the United States in 1995. The mechanism(s) of action of metformin is not fully understood but it is suggested that it potentiates AMP-dependent protein-kinase (AMPK), a family of enzymes involved in intracellular energy homeostasis, carbohydrate and lipid metabolism, insulin secretion, and appetite.<sup>61,62</sup> Metformin's primary effect is widely quoted as antihyperglycemic as a result of suppression of hepatic gluconeogenesis,<sup>63</sup> although the potential beneficial effects of metformin are far wider than suppression of hyperglycemia. Other insulin-mediated effects of metformin include increased glucose uptake in peripheral tissues and reduction of plasma triglyceride concentrations suggesting a widespread insulin-sensitizing effect.<sup>64-66</sup> Furthermore, in the UK Prospective Diabetes Study, metformin was found to have a superior protective effect on the cardiovascular complications of IR in human subjects despite a similar degree of glycemic control compared with other drugs.<sup>67</sup> Moderation of endothelial hemostatic factors has

been attributed to an endothelioprotective effect of metformin.<sup>68</sup> In contrast to other pharmacologic therapies for human IR, modest weight loss is a further unique benefit of metformin therapy in humans.<sup>67</sup>

The optimal dose of metformin in humans is approximately 25 mg/kg/d in 2 or 3 divided doses.<sup>69</sup> A study in obese mares found no convincing effect of metformin on insulin sensitivity when administered in doses up to 8.4 mg/kg by mouth twice a day.<sup>70</sup> A more recent study of 18 recurrently laminitic horses and ponies found a more favorable effect of metformin on estimates of IR and clinical signs of laminitis when administered at a dose of 15 mg/kg by mouth twice a day.<sup>71</sup> Fasting insulin and glucose and derived proxies were significantly improved in 10/11 subjects within 2 weeks of commencing therapy although this effect was not sustained in several of these. Studies conducted in human patients treated with metformin have generally reported significant decreases in circulating concentrations of glucose and insulin<sup>72,73</sup> although, as mentioned earlier, the potential benefits of metformin extend beyond insulin-glucose metabolism. Despite frequent gastrointestinal symptoms in human patients treated with metformin, no adverse effects of oral therapy have been reported in horses.<sup>70,71,74,75</sup> However, recent pharmacokinetic studies in horses have revealed poor bioavailability of metformin indicating the necessity for further evaluation of dosages and pharmacologic effects.<sup>74,75</sup>

### **Thiazolidinediones**

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The thiazolidinediones (TZDs) pioglitazone and rosiglitazone are 2 further insulin-sensitizing drugs commonly prescribed for humans.<sup>66</sup> TZDs are also suspected to promote AMPK although their major mode of action is more likely via stimulation of peroxisome proliferator-activated receptor gamma, a nuclear transcription factor that promotes genes involved in regulating glucose and lipid metabolism.<sup>66</sup> The main effect of TZDs seems to be increased glucose uptake by skeletal muscle cells and decreased lipolysis, typically increasing insulin sensitivity by 25% to 68%.<sup>76,77</sup> TZDs also lead to increased adiponectin synthesis (an insulin-sensitizing hormone), antiinflammatory effects, and improved endothelial function and fibrinolytic activity.<sup>78–81</sup> Comparative studies indicate a greater peripheral insulin-sensitizing effect and better control of hyperinsulinemia with TZDs compared with metformin in human subjects.<sup>72,73</sup> However, in contrast to metformin, treatment with TZDs is expensive, and associated with undesirable weight gain. Health concerns regarding hepatotoxicity and cardiovascular risk have also been published.<sup>82–85</sup>

### **SUMMARY**

The treatment of endocrinopathic laminitis entails general therapeutic and management protocols applicable to other forms of laminitis. Targeting the underlying endocrinopathy is a further prophylactic aim of therapy and can be effectively accomplished in PPID cases with pergolide and, should this prove to be unsuccessful, alternative agents such as bromocryptine, cyproheptadine, and trilostane can be used. The preferred pharmacologic approach in obese EMS cases is L-thyroxine supplementation although further investigation of insulin-sensitizing agents such as metformin might bring about additional therapeutic options.

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