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Hyperinsulinaemia

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The role of hyperinsulinaemia in the development of laminitis

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Laminitis usually occurs as a consequence of 3 broad categories of disorders: systemic inflammation, endocrine disturbances or trauma. By far the majority of research on laminitis has been associated with inflammatory models of laminitis including the carbohydrate overload with starch or oligofructose models and the inflammatory (Black Walnut) model.

Endocrinopathic laminitis has been defined as laminitis developing from hormonal influences and not pro-inflammatory or intestinal conditions (Johnson *et al.* 2004). Conditions associated with endocrinopathic laminitis include Equine Metabolic Syndrome (EMS), pasture-associated laminitis or prelaminitic equine metabolic syndrome, Equine Cushing's Syndrome (ECS) also called pituitary pars intermedia dysfunction (PPID) and iatrogenic corticosteroid administration. Common to all are disturbed glucose and insulin regulation resulting in the development of insulin resistance and hyperinsulinaemia which has been shown both in field studies (McGowan *et al.* 2004; Treiber *et al.* 2006) and in experimental studies (Asplin *et al.* 2007; de Laat *et al.* 2010).

A recent shift in opinion about laminitis has been the realisation that endocrinopathic is by far the most common form of laminitis. This has prompted increasing interest in endocrine events resulting in laminitis. Horses that suffer endocrinopathic laminitis differ from those with systemic inflammation in that they are not systemically unwell, are not pyrexic and do not have alterations in gastrointestinal function. Insulin has been shown to be a final triggering event in causing endocrinopathic laminitis in both ponies and horses. Laminitis could be induced in 100% of ponies or horses exposed to high concentrations of insulin (approximately 1000 µiu/ml) while maintaining normal blood glucose concentrations within normal reference ranges using a modified euglycaemic-hyperinsulinaemic clamp technique (Asplin *et al.* 2007; de Laat *et al.* 2010). All ponies and horses were healthy, young and nonobese, with no history of laminitis and no evidence of endocrine or other abnormalities on blood tests.

These studies have shown the crucial role insulin plays as an important trigger of endocrinopathic laminitis. Of importance is that the induction of laminitis occurred independently of glucose or (direct) dietary factors, and also without any evidence of gastrointestinal disturbance. Horses and ponies in the study had routine blood tests performed both before and at the onset of laminitis and no changes were found, nor were there any clinical signs indicative of system illness or inflammation.

Insulin levels reached in these experiments were higher than typically seen in grazing horses with prelaminitic metabolic syndrome (Treiber *et al.* 2006). However, insulin values over 1000 µiu/ml have been reported in naturally occurring cases of severe EMS (Reeves *et al.* 2001; McGowan and Riley 2004). Whether the effect is the same for longer term exposure to lower levels of insulin or not remains to be determined with further study.

Interestingly, despite the lack of systemic or gastrointestinal clinical illness, endocrinopathic laminitis may also involve some of the same mechanisms as those occurring in inflammatory laminitis. However, some important differences are emerging which have prompted a re-evaluation of what we had previously thought applied to all cases of laminitis.

1. Histological changes were milder and leucocyte emigration was significantly less in horses with insulin-induced laminitis than horses developing laminitis secondary to carbohydrate overload (de Laat *et al.* 2011a). Insulin-induced lesions at Obel *grade 2* lacked widespread basement membrane degradation, especially in ponies. Instead there were cellular changes and stretching/elongation of secondary (but not primary) epidermal lamellae (Asplin *et al.* 2010).
2. Supporting the lack of widespread basement membrane degradation was the finding that matrix metalloproteases (MMP-2, MT1-MMP, TIMP-3 and ADAMTS-4) were not upregulated in the insulin-induced model and that increases in MMP9 only were detected after 48 h corresponding to the neutrophil infiltration of the lamellae (i.e. a later event) (de Laat *et al.* 2011b).

For practitioners, the information from research into endocrinopathic causes of laminitis has direct implications on laminitis management. In all cases of laminitis where evidence of systemic inflammation/gastrointestinal disease or trauma has not been found, horses should be suspected as endocrinopathic and appropriate endocrine testing carried out. For those horses <15 years of age and with no evidence of ECS, this will predominantly involve tests for basal insulin concentration and insulin resistance. Basal insulin values are often all that is required for native British breeds, but practitioners should be prepared to perform dynamic endocrine testing to support a diagnosis where basal testing is unsupportive. Where endocrinopathic laminitis has been confirmed, treatment should also include monitoring and treatment of the underlying endocrinopathy.

References and further reading

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