

# Chapter **6** The Glucose Theory of Laminitis

---

## **Changes in glucose metabolism as a trigger for laminitis**

Hoof lamellar explants kept in tissue culture medium consume glucose and readily separate when glucose is absent from the culture medium. It seems that, after removal from the horse, hoof tissue is reliant on glucose for maintenance of adhesion between the epidermal lamellae and the basement membrane. The addition of compounds to the culture medium which block lamellar energy production from glucose cause lamellar separation (*in vitro* laminitis).

The major feature of the acute metabolic stress that attends acute fulminating diseases such as colitis, metritis and carbohydrate alimentary overload is that glucose consumption in many peripheral tissues is reduced. The purpose of this change is to maintain glucose, and therefore energy supplies, to the vital organs (heart, lung and brain) at the expense of other tissues. Metabolic stress is regulated by the hormones insulin, glucagon, cortisol and adrenaline. Insulin promotes glucose utilisation, glucagon promotes glucose production, especially by the liver, cortisol and adrenaline promote glucose production from other substrates and reduce glucose consumption in peripheral tissues such as skin and hoof. *In vitro* studies show that hoof tissues are extremely reliant on glucose and the rapidly decreasing local concentrations of glucose that accompany severe physiological stress could mimic the *in vitro* situation and cause lamellar separation via the triggering of lamellar MMP production. Other epithelia may be similarly weakened, but gross separation would be manifest most readily in the hoof because of the large mechanical forces generated by weight bearing.

There is evidence that the metabolic changes described above do occur as a consequence of carbohydrate overload in horses developing laminitis. During the development of laminitis, an increase in blood cortisol, consistent with a metabolic change to conserve glucose, occurs. Failure of the lamellar basement membrane may be occurring via two mechanisms: lamellar MMP activation (due to arrival of bacterial laminitis trigger factors)

and hemidesmosome dissolution (due to failure of lamellar basal cell glucose uptake).

### **Equine Cushing's disease**

Older ponies and horses sometimes develop a problem with their pituitary gland which is situated at the base of the brain. The gland enlarges and becomes dysfunctional, resulting in the development of Cushing's syndrome. The enlargement is sometimes described as a tumour (pituitary adenoma), but most are cases of pituitary hyperlasia (an increase in size for unexplainable reasons). The region of the pituitary involved is the *pars intermedia* giving the condition its common medical name; pars intermedia adenoma (PIA). The dysfunctional pituitary produces an excess of hormones and peptides that control other hormones. A sign that horses are affected by PIA is hirsutism; the hair coat grows unnaturally long and is not shed at the usual times (**Figure 6.1**). The hormone imbalance also creates a tissue resistance to insulin that disturbs glucose uptake in hoof lamellae and an insidious, relentlessly developing, chronic laminitis. Affected horses and ponies often have higher than normal concentrations of glucose, cortisone and insulin in their blood. The levels of these substances varies throughout the day (diurnal or circadian rhythm) and care has to be taken with the interpretation of blood analysis. The laminitis developed by animals with Cushing's disease is usually refractory to treatment. However promising results have been obtained after the administration of pergolide mesylate (Permax), a drug registered for human use. Doses in the range of 1-2mg/horse/day have been recommended. The drug mechanism is to reduce production, in the pituitary gland, of the hormone (ACTH) that controls cortisol production in the adrenal gland. With cortisol under control, insulin responsiveness in hoof lamellae returns and the laminitis stabilises.

### **Hyperlipaemia**

Further support for a relationship between changes in glucose metabolism and laminitis comes from observations on ponies and horses with hyperlipaemia. Hyperlipaemia is a state of negative energy balance occurring rapidly, and often precipitated by some form of stress. It has been suggested that the laminitis caused during hyperlipaemia is a result of vasoconstriction in the hoof as a consequence of the altered metabolism in the animal. An alternative explanation is that the metabolic changes leading to hyperlipaemia result in the hoof tissues being starved of glucose, thus precipitating the chain of events leading to triggering of MMP production and separation of the hoof lamellae, as occurs in cultured explants.



◀FIGURE 6.1 Pony with Equine Cushing's Disease showing hirsutism. A dysfunctional pituitary produces, in excessive amounts, hormones and peptides that control other hormones. The hormone imbalance also creates a tissue resistance to insulin that disturbs glucose uptake in hoof lamellae and causes chronic laminitis. A sign that horses are affected, in addition to chronic laminitis, is hirsutism.

### Supporting limb laminitis

Laminitis in the lamellae of a single hoof can occur whenever a horse's limb is forced to bear weight unilaterally for prolonged periods of time. This can occur when an injury (bone or joint fracture) or disease process (septic arthritis) in the contralateral limb is so painful that weight bearing is impossible. After 2-3 days of unrelieved weight bearing, the supporting limb develops lamellar pathology, often to a severe degree. The case for ischaemia as the cause of supporting limb laminitis appears to be clear cut. The evidence comes from *in vitro* studies using digitised subtraction angiography (DSA) in isolated perfused horse limbs (obtained after humane slaughter at a knackery). When a mechanical press was used, to place the limb in the loaded, (fetlock fully extended) position, there was zero perfusion of the foot below the level of the coronary band. When the limb was not loaded perfusion through all the major vessels of the foot was normal. Presumably a similar situation prevails *in vivo* and chronic lack of perfusion eventually triggers a lamellar pathology indistinguishable from that initiated by other causes. This form of laminitis may be prevented if the supporting limb is firmly wrapped in an elastic support bandage and shod with an effective support shoe. The horse should be provided with a deep bed of wood shavings or sand so that it can lie down comfortably and allow blood to circulate through its feet. Deep, compliant bedding

also allows the horse to find a foot position that promotes the circulation. The injured limb should be treated promptly and fitted with a cast or splint so that it can begin to take its share of weight bearing. Pain should be controlled with analgesics for the same reason.

### **Key Points**

- Lack of glucose has been implicated as another cause of the separation of the basement membrane from the epidermal lamellae.
- Equine Cushing's disease involves tissue resistance to insulin that alters glucose uptake in hoof lamellae and results in chronic laminitis. Hyperlipaemia also causes laminitis, perhaps caused by low glucose concentrations in hoof tissue.
- Supporting limb laminitis, in the lamellae of a single hoof, can occur whenever one leg is required to bear weight unilaterally for extended periods of time. Preventative treatment should be used to avert the development of laminitis in the weight-bearing foot.