MESSAGE FROM THE GRAYSON-JOCKEY CLUB RESEARCH FOUNDATION

THE LATEST ON LAMINITIS STUDIES

Grayson-Jockey Club Research Foundation

BY DR. TERESA BURNS

LAMINITIS IS A CRIPPLING disease of equids that represents a major cause of economic loss and humane concern in equine populations worldwide. It is a critically important priority for equine research due to the high incidence of the disease (annual incidence of 2–7% of horses in recent studies), the pain induced by the condition (often resulting in euthanasia or loss of use), and the lack of effective therapies for treating it.

While laminitis can be a complication of several diverse conditions in equids (including colic, diarrhea, pneumonia, and severe lameness), endocrine disease (such as equine metabolic syndrome and PPID) is by far the most common underlying cause of laminitis worldwide today, accounting for almost 90% of laminitis cases attended by equine veterinarians. Similar to human metabolic syndrome, equine metabolic syndrome is now known to affect not only obese animals, but also horses maintained in ideal body condition for their occupation or breed. Abnormalities of insulin and glucose dynamics (commonly referred to as 'insulin dysregulation' or ID) have a strong association with lamellar injury and are a primary therapeutic target for equine patients with endocrinopathic laminitis.

Nutritional management and aerobic exercise are central to treatment of EMS, but both can be difficult in the face of refractory ID and the severe pain of laminitis, especially in genetically predisposed breeds (such as ponies, Arabians, and gaited breeds, for example). Thus, in addition to dietary and exercise management, it is critical to establish medications that improve ID in animals at risk for or already suffering from endocrinopathic laminitis; drugs that both improve systemic ID and protect the digital lamellae are particularly attractive prospects.

Many of the drugs available for treating ID activate important metabolic signaling pathways, such as a protein called AMPK (5'-adenosine-monophosphate-activated protein kinase) that is present in virtually all cells of the body. This protein has been referred to as "exercise in a bottle," and drugs that activate it might be particularly useful for improving ID in foundered horses that can't work due to foot pain. These drugs are used extensively in human medicine to treat metabolic syndrome and type II diabetes (metformin is an example), where they improve insulin and glucose dynamics.

Further, activation of AMPK has been shown to support the health of epithelial cells and foster the connections between them; these are the very cells that are critical for providing the strength of the equine digital lamellae in supporting the weight of the horse (and that fail in the setting of laminitis). AMPK is therefore an attractive therapeutic target in endocrinopathic laminitis, but few drugs that activate this enzyme have been critically evaluated in horses for this purpose, particularly when used in combinations. Several of them, however (such as aspirin, metformin, and resveratrol), have been safely used in horses for other purposes and are available on the market for veterinary use.

Our laboratory is interested in identifying drug therapies that are safe and effective for the treatment and prevention of equine ID and endocrinopathic laminitis. In a study supported by the Grayson Jockey Club Research Foundation, our research team has recently shown that two AMPK-activating drugs, metformin and aspirin, act synergistically (greater effect than either drug alone) to improve insulin and glucose dynamics when administered as a combination to adult light-breed horses with dexamethasone-induced ID. Resveratrol, another AMPK-activating drug that acts like metformin and aspirin, would be another attractive therapeutic option for equine ID, given that resveratrol is safe, palatable, and economical, with products already on the market. It also might be even more effective against ID when given in combination with metformin and aspirin, but this hasn't been evaluated in horses to date.

In a follow-up study supported by GJCRF, we plan to evaluate resveratrol, aspirin, and metformin combinations in the same model of dexamethasone-induced ID. If resveratrol further enhances the ability of the metformin/aspirin combination to improve ID, this will provide support for a novel combination medical approach; if resveratrol given alone is as effective as the metformin/aspirin combination, then a simplified approach using only one medication (that is also palatable and well-tolerated) might be feasible.

We are hopeful that this work will result in the establishment of a novel therapeutic protocol involving safe and economical medications, given easily by mouth, which can improve insulin and glucose dynamics in horses with ID. These drugs will then be another tool that enhances our ability to prevent endocrinopathic laminitis in horses at risk, treat laminitis in horses already suffering from it, and improve the health and well-being of the horse. BH

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