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Evaluation of muscle calcium regulation in recurrent exertional rhabdomyolysis using a cell culture model derived from equine skin

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Background

- **Exertional rhabdomyolysis**, aka “tying up” and “Setfast” is a painful muscle condition that affects approximately 5% of Thoroughbred racehorses.
 - The mechanism that leads to muscle cell damage is not understood.
 - Improved understanding may help lead to the disease’s cause and improved treatments.
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Reasons for the study

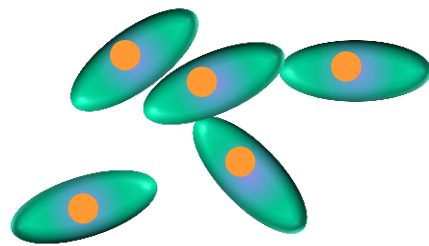


- To evaluate a potential mechanism that may account for tying up in Thoroughbred racehorses.
 - To investigate the mechanism by which a commonly administered drug (dantrolene) may work.
 - To generate a bank of cells that can be used for future research thereby avoiding need for further animal experimentation.
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What we did

- Using genetic engineering in the laboratory, we converted horse skin cells from a small biopsy into muscle cells and studied the cells' calcium regulation.

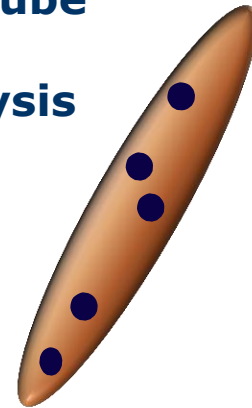


**Fibroblasts
from skin
sample**

MyoD



**Myotube
for
analysis**





What we found

- We found no differences in the way calcium was handled in horses that tie-up.
 - We showed that dantrolene lowers the resting calcium concentration inside a horse muscle cell, which may account for its efficacy.
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Conclusions and potential relevance to the Thoroughbred



- Future research on the cause of tying up should concentrate on alternative mechanisms.
 - This cellular model is applicable to a wide range of experiments looking for the causes of tying up.
 - We have generated a bank of cells that can be used for these purposes.
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Scientist's Summary

- In this project we sought to determine whether exertional rhabdomyolysis in Thoroughbred racehorses is similar to a disease in humans and other species, known as malignant hyperthermia.
 - In particular, we collected skin samples from Thoroughbred horses with and without a susceptibility to tying up. From these samples we cultured cells that were converted to muscle cells in the laboratory.
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Scientist's Summary

- We were then able directly to evaluate the manner in which calcium was controlled inside a living muscle cell from each horse.
 - We demonstrated defects in calcium handling in cells derived from human and equine patients with a known calcium handling defect (malignant hyperthermia), but found no such similar defect in horses that tie-up.
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Scientist's Summary

- This means that it is most likely that an alternative explanation accounts for the reason that Thoroughbred horses tie up.
 - Dantrolene is a commonly-used drug for treating tying up. In related studies, we have demonstrated the likely mechanism by which this medication works.
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