Role of Sympathetic Denervation in the Development of Vascular Calcification
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Introduction

Current Knowledge: Vascular calcification is an active process driven by transdifferentiation of vascular smooth muscle cells (VSMCs) from contractile to osteo/chondrogenic phenotypes. VSMCs are innervated in healthy conditions and rely on many types of signaling to maintain phenotype.

Problem: Calcification pathogenesis is not fully characterized, making treatment development difficult.

Goal: Develop a sympathetic denervation animal model to study the impact of disrupted nerve signals on calcification.

Hypothesis: Sympathetic denervation will disrupt signals to VSMCs that help maintain a contractile phenotype, leading to osteogenic transdifferentiation.

Methods

Animals*: 4 to 14-week-old male BALB/c mice (n = 8 total)
Artery: Femoral artery
Neurotoxin: 6-hydroxydopamine (6-OHDA)

Procedure: Artery was successfully separated from the nerve bundle and stained with H&E. Artery labeled with white arrow, and nerve bundle with yellow arrow. Scale bar: 50 μm.

Results

• Artery was successfully separated from the nerve bundle
• 100% survival rate
• Optimization of harvest, paraffin embedding, and sectioning technique completed

Discussion

Initial Denervation
Denervation of murine femoral arteries with 6-OHDA was successfully achieved by one week.

Sympathetic Nerve Presence
Preliminary data from the animals sacrificed at two weeks shows no obvious reduction in innervation in the injured tissue compared to the control, possibly signifying nerve regeneration or axonal growth.

Possible Causes
Nerve regeneration or growth has been shown to occur in rabbits four weeks after treatment with 6-OHDA.[3] Artemin is one factor that may play a role, as it is known to promote migration, proliferation, and differentiation of sympathetic neuron precursors.[4]

Conclusions

1. 6-OHDA is a viable sympathetic neurotoxin for mouse femoral artery denervation for up to one week.
2. Denervation is reversed at two and four weeks after treatment with 6-OHDA.
3. Further investigation is necessary to determine if denervation period can be prolonged and if this injury can cause calcification.

Future Directions

• Artemin in vitro studies (siRNA)
• Surgical Adjustments
  • 6-OHDA application time
  • 6-OHDA reaplication
  • Include Female Animals

References


*All animal work approved by Northwestern IACUC