ANGIOTENSIN RECEPTOR BLOCKERS IMPROVE MUSCLE REGENERATION AND DECREASE FIBROSIS IN INJURED SKELETAL MUSCLE

*Bedair, H S; *Li, Y; +*Huard, J
+*Growth and Development Laboratory, Children's Hospital of Pittsburgh and Department of Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, PA
jhuard@pitt.edu

INTRODUCTION:

Skeletal muscle injuries are the most common ailments treated by orthopaedic surgeons. Muscle undergoes a natural process of healing and regeneration. However, the formation of fibrous tissue often causes this process to end before complete recovery [1]. This incomplete recovery, in turn, predisposes the muscle to re-injury and impaired function. Patients treated with angiotensin receptor blockers (ARBs) have exhibited reduced fibrosis and improved function in many organs affected by fibrotic disease processes, including the heart, liver, kidneys, and lungs [2–5]. The aim of this study was to investigate the effect of losartan, an ARB, on skeletal muscle healing after injury.

MATERIALS AND METHODS:

In this study, 40 mice underwent bilateral gastrocnemius lacerations. Mice then were assigned randomly to a control group (tap water), a low dose losartan group (0.05mg/mL), or a high dose losartan group (0.5mg/mL); losartan was dissolved in the drinking water for the entirety of the study, and water consumption was monitored. Mice were sacrificed 3 or 5 weeks after injury, and the lacerated muscles were examined histologically. Immunohistochemistry was used to compare the distribution of angiotensin II receptors within injured and non-injured muscle tissue. Hematoxylin and eosin staining was used to determine the average number of regenerating myofibers (centronucleated fibers) per high-power field within the area of injury. Trichrome staining and imaging software (Northern Eclipse) were used to calculate the percent fibrous tissue within the zone of injury.

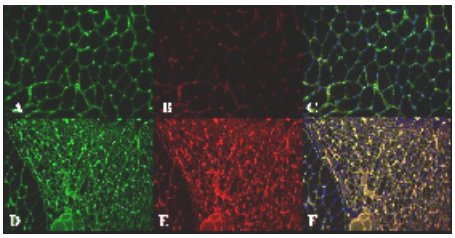
RESULTS:

We observed an up-regulation of angiotensin II receptors in injured tissue compared with non-injured tissue; these receptors colocalized with areas of dense collagen IV deposition (Fig. 1). Compared with control mice at 3 and 5 weeks, losartan-treated mice exhibited significantly more regenerating myofibers (with a dose-dependent trend; Fig. 2, *P<0.05, **P<0.01). Compared with control mice at 3 and 5 weeks, the losartan-treated mice also developed significantly less fibrous scar tissue within the area of injury (with a dose-dependent trend; Fig. 3, *P<0.05, **P<0.01). The losartan-treated groups demonstrated a decreased rate of fibrosis during the study. In addition, an inverse relationship existed between fibrosis and muscle regeneration.

DISCUSSION AND CONCLUSIONS:

This study demonstrates the up-regulation of angiotensin II receptors in areas of fibrous skeletal muscle after injury. These receptors appear to represent one pathway involved in the formation of fibrous tissue. By modulating the response of these receptors to local and systemic angiotensin II, ARB therapy significantly reduced fibrosis and led to an increase in the number of regenerating myofibers. These effects were apparent as early as 3 weeks after injury in mice treated with sub-therapeutic (anti-hypertensive) doses of losartan.

Many highly experimental therapies have been demonstrated to improve muscle healing; however, this study is the first to employ a safe and commonly used medication in a novel manner to improve muscle healing after injury. The clinical implications for this application of losartan are potentially far-reaching, and include not only sports-related injuries but also diseases like the muscular dystrophies, in which the formation of fibrous tissue within skeletal muscle is severely debilitating.



Non-injured skeletal muscle

Injured skeletal muscle

Figure 1. Immunohistochemistry: A) collagen IV, B) angiotensin II receptor, and C) colocalized image from non-injured skeletal muscle; D) collagen IV, E) angiotensin II receptor, and F) colocalized image from injured skeletal muscle.

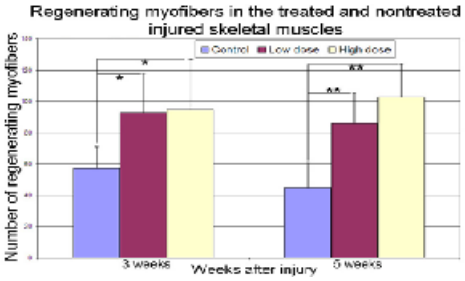


Figure 2.

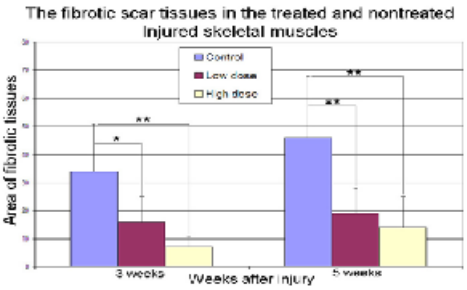


Figure 3.

ACKNOWLEDGMENTS:

This research was supported in part by the NIH (R01 AR 47973-01), the William F. and Jean W. Donaldson Chair at Children's Hospital of Pittsburgh, the Henry J. Mankin Endowed Chair at the University of Pittsburgh, and the Hirtzel Foundation.

REFERENCES :

1. Huard J, Li Y, Fu F. J Bone Joint Surg Am 2002;84-A(5):822–32.
2. Paizis G, Gilbert RE, Cooper ME, et al. J Hepatol 2001;35(3):376–85.
3. Lim DS, Lutucuta S, Bachireddy P, et al. Circulation 2001;103(6):789–91.
4. Suga S, Mazzali M, Ray PE, et al. Kidney Int 2002;61(3):951–8.
5. Otsuka M, Takahashi H, Shiratori M, et al. Thorax 2004;59(1):31–8.