Angiotensin 2 receptor blockers suppress oxidative stress in human rotator cuff cells

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INTRODUCTION: Recently, it has been observed that advanced glycation end products (AGEs) cause tissue fibrosis, mainly through abnormal bridging of collagen and oxidative stress. In shoulder rotator cuff tissue, AGEs have also been noted to decrease cellular activity and increase reactive oxygen species (ROS)[1]. There have been scattered reports of drugs that reduce the effects of AGEs, and angiotensin II receptor blockers (ARBs), which are used to treat cardiovascular diseases such as heart failure and hypertension, have also been reported to inhibit AGE production in the past[2]. However, the effect of ARBs on rotator cuff-derived cells has not been reported. Therefore, the purpose of this study was to evaluate the in vitro effects of ARB (losartan) on human rotator cuff-derived cells.

METHODS: Rotator cuff tissue was harvested from the injured edge of the supraspinatus tendon from 10 patients with rotator cuff tears who had no history of ARB medications at the time of arthroscopic rotator cuff repair. The harvested rotator cuff tissues were cultured in DMEM medium. The 2nd~4th passages of human rotator cuff cells were cultured in normal medium or hyperglycemic medium for 2 days. Cell groups were also prepared by adding ARB to each medium and divided into 4 groups (control group: C group, control + ARB group: CL group, hyperglycemia-loaded group: H group, hyperglycemia-loaded + ARB group: HL group). Gene expression (RT-PCR), cell viability, intracellular ROS production and apoptosis cell ratio were evaluated.

RESULTS SECTION: The concentrations of ARBs used ranged from 0.1~1000 μM, and the concentration of ARBs used was determined by cell viability to be 100 μM. Gene expression of NOX1, NOX4, IL-6, IL1β, and AGEs receptor (RAGE) was higher in the H group than in the other groups. Cell viability was significantly lower in the H group than in the other groups. ROS production was lower in the CL and HL groups than in the C and H groups. No significant difference in the apoptosis cell ratio was observed.

DISCUSSION: The results of this study showed that stress with hyperglycemic medium increased gene expression of NOX1, NOX4, IL-6, IL1β, and RAGE in rotator cuff-derived cells. Activation of NOX also increased ROS production and deteriorated cell viability. On the other hand, ARBs may exert inhibitory effects on AGE-induced oxidative stress in rotator cuff-derived cells.

SIGNIFICANCE: ARBs may improve rotator cuff tissue function by reducing oxidative stress on rotator cuff derived cells.

REFERENCES:
[1] Mifune Y, et al. Influence of advanced glycation end products on rotator cuff. JSES. 2019.
[2] Miyata T, et al. Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: biochemical mechanisms. J Am Soc Nephrol. 2002

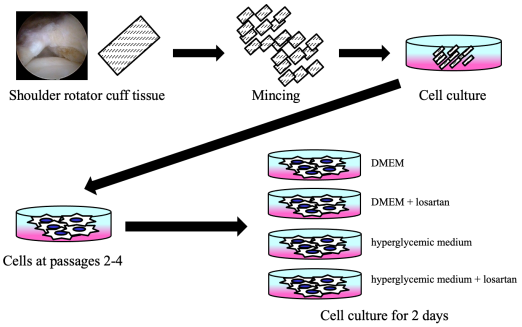

Figure 1. Cell culture protocol for this study.

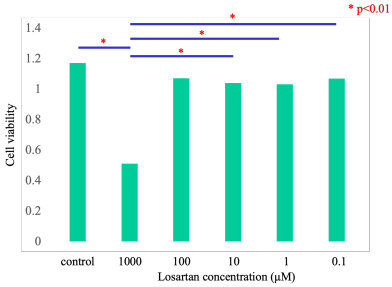

Figure 2. Cell viability for determining losartan concentration.

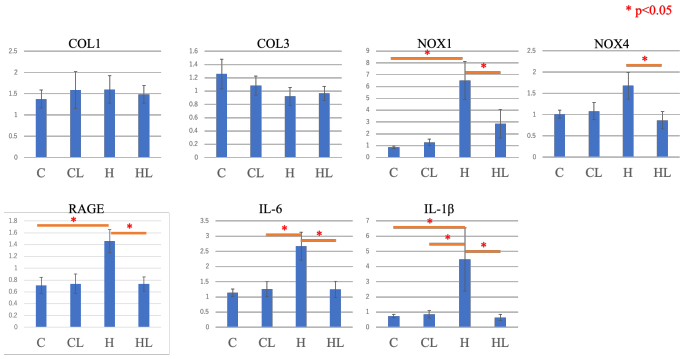

Figure 3. Gene expressions for each group.