November 2011 - Volume 21 - Issue 11

- Previous Abstract
- Next Abstract

ORIGINAL ARTICLES

Ramipril modulates circadian gene expression in skeletal muscle

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Abstract

Objectives

Treatment with angiotensin converting enzyme (ACE)-inhibitors favorably affects glucose metabolism and the development of diabetes mellitus by largely elusive mechanisms. To identify these mechanisms, we studied the effect of ACE-inhibition on gene expression in skeletal muscle, a primary target tissue for insulin in glucose homeostasis.

Methods

A subject-blinded and analyst-blinded, placebo-controlled study was conducted in nine healthy men. Two consecutive muscle biopsies were conducted before and 9 h after a single dose of either 10-mg ramipril (n=6) or placebo (n=3), (randomly allocated). Muscle ribonucleic acid was subjected to transcriptome profiling.

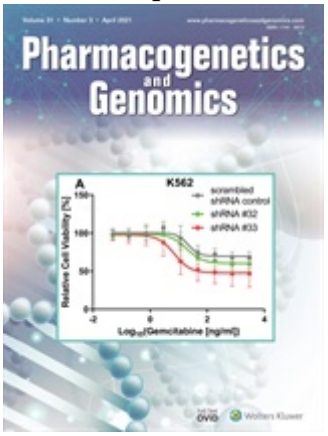
Results

In both ramipril-treated or placebo-treated individuals, the majority of genes with differential expression between the two time points belonged to the family of diurnally regulated genes, such as the *NR1D1* and *NR1D2* genes (nuclear receptor subfamily 1, group D, members 1 and 2) or members of the period homolog family (*PER1-3*). Ramipril significantly modulated the expression of other diurnally regulated genes, such as aryl hydrocarbon receptor nuclear translocator-like (*ARNTL*), encoding aryl hydrocarbon receptor nuclear translocator-like, a core component of the circadian clock (P=0.02). Concomitant attenuation of *NR1D1* downregulation (−2.4-fold compared with −4.1-fold in placebo; P=0.04), a transcriptional repressor of *ARNTL*, supported the view that ramipril might modulate glucose homeostasis pathways involving the *NR1D1 ARNTL* axis.

Conclusion

As circadian rhythms are deranged in patients who are diabetic, modulated expression of circadian clock genes by ramipril could explain the favorable metabolic effects of therapeutic ACE-inhibition.

^Back to Top



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