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Insulin-like growth factor-1 mediates stretch-induced upregulation of myostatin expression in neonatal rat cardiomyocytes

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Abstract

Objectives: Myostatin, a negative regulator of muscle growth, is increased in hypertrophied and infarcted heart. However, the mechanism of regulation is not known. Mechanical stress is an important regulatory factor for cardiomyocyte growth. The aim of the study was to investigate the effect of cyclic stretch on the expression of myostatin gene in cardiomyocytes.
Methods: Neonatal Wistar rat cardiomyocytes grown on a flexible membrane base were stretched by vacuum to 20% of maximum elongation at 60 cycles/min. An in vivo model of aorta-caval shunt in adult rats was used to investigate the myostatin expression.
Results: Cyclic stretch significantly increased myostatin protein and mRNA expression after 6 to 18 h of stretch. Addition of the p38 mitogen-activated protein (MAP) kinase inhibitor SB203580, insulin-like growth factor-1 (IGF-1) monoclonal antibody, and p38 siRNA 30 min before stretch inhibited the induction of myostatin protein. Cyclic stretch increased, while SB203580, IGF-1, and IGF-1 receptor antibody abolished, the phosphorylated p38 protein. Gel shift assays showed significant increase of DNA-protein binding activity of myocyte enhancer factor 2 (MEF2) after stretch, and transfection with p38 siRNA abolished the DNA-protein binding activity induced by cyclic stretch. Cyclic stretch significantly increased the IGF-1 secretion from myocytes. Both conditioned media from stretched myocytes and exogenous administration of IGF-1 recombinant protein to the non-stretched myocytes increased myostatin protein expression similar to that seen after cyclic stretch. An in vivo model of aorta-caval shunt in adult rats also demonstrated the increased myostatin expression in the myocardium.
Conclusions: Cyclic mechanical stretch enhances myostatin expression in cultured rat neonatal cardiomyocytes. The stretch-induced myostatin is mediated by IGF-1 at least in part through a p38 MAP kinase and MEF2 pathway.

Keywords: Myostatin; Insulin-like growth factor-1; Myocytes; Cyclic stretch; p38 MAP kinase

This article is referred to in the Editorial by Gaussin and Depre (pages 347–349) in this issue.

1. Introduction

Myostatin is a transforming growth factor-β family member that plays an essential role in regulating skeletal muscle growth [1]. Myostatin, a negative regulator of muscle growth, is highly conserved across species [2]. Although myostatin was first characterized in skeletal muscle, it has also been identified in the heart [1,3–5]. Sharma et al. demonstrated that myostatin is expressed in

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