

News Release

Title

The new mechanism of cardioprotection by endurance exercise

~Identification of the cardioprotective hormone derived from skeletal muscle~

Key Points

- Myonectin functions as a skeletal muscle-derived hormone which ameliorates acute myocardial ischemia-reperfusion injury by suppressing apoptosis and inflammation in the heart.
- Endurance exercise attenuates myocardial ischemia-reperfusion damage in mice, at least in part, through induction of myonectin production.
- Myonectin is a cardioprotective hormone, which partly mediates the cardiovascular benefits of endurance exercise, suggesting that myonectin represents a target molecule for prevention or treatment of ischemic heart disease.

Summary

Prof. Noriyuki Ouchi at Department of Molecular Medicine and Cardiology, Nagoya University Graduate School of Medicine (Dean: Prof. Kenji Kadomatsu), Prof. Toyoaki Murohara at Department of Cardiology, Nagoya University Graduate School of Medicine, Dr. Naoya Otaka at Department of Cardiology, Nagoya University Graduate School of Medicine, and their collaborators identified the skeletal muscle-derived hormone which can ameliorate acute myocardial ischemia-reperfusion injury and demonstrated the important role of this hormone in exercise-induced cardioprotection.

Exercise training exerts favorable effects on prevention and treatment of cardiovascular diseases. However, the molecular mechanisms of cardiovascular benefits of exercise are incompletely understood. Here, we investigated the role of the skeletal muscle-derived hormone, myonectin, in regulation of myocardial ischemic injury. Myonectin-knockout (KO) mice showed enhancement of myocardial infarct size, cardiac dysfunction, apoptosis and inflammatory response following ischemia-reperfusion compared with wild-type (WT) mice. Treadmill running exercise increased circulating myonectin levels in WT mice, and it reduced infarct size following ischemia-reperfusion in WT mice, but not in myonectin-KO mice. Mechanistically, myonectin reduces cardiomyocyte apoptosis and macrophage inflammatory response, thereby contributing to improvement of myocardial ischemia-reperfusion injury. These data indicate that myonectin functions as an endurance exercise-induced hormone which ameliorates acute myocardial ischemic injury by suppressing apoptosis and inflammation in the heart, suggesting that myonectin can partly mediate the cardiovascular benefits of endurance exercise. This work was published online in *Circulation Research* on September 12, 2018.

Research Background

Cardiovascular disease including ischemic heart disease is the major cause of morbidity and mortality worldwide. Physical exercise benefits for a variety of organs including the cardiovascular system. Particularly, endurance exercise training is an effective lifestyle intervention to reduce cardiovascular risk. However, the molecular mechanisms of the cardiovascular protective actions of exercise are incompletely understood.

Recent evidence indicates that skeletal muscle produces a variety of hormonal factors, also referred to as “myokines”, which can contribute to the pathogenesis of metabolic and cardiovascular disorders. However, nothing is known about the endurance exercise-regulated myokine that directly affects the development of cardiovascular disorders.

Research Results

We focused on the myokine, myonectin, which is abundantly expressed in skeletal muscle tissue and investigated its role in regulation of myocardial ischemic injury. Myonectin-knockout (KO) mice showed enhancement of myocardial infarct size, cardiac dysfunction, apoptosis and inflammatory response following ischemia-reperfusion compared with wild-type (WT) mice. Thus, myonectin may protect the heart from ischemic injury by suppressing apoptosis and inflammatory reactions.

Treadmill running exercise increased circulating myonectin levels in WT mice and reduced infarct size following ischemia-reperfusion in WT mice. Importantly, the protective actions of treadmill exercise on myocardial ischemic injury were diminished in myonectin-KO mice. Therefore, it is conceivable that myonectin is involved in cardioprotection by endurance exercise.

Transgenic overexpression of myonectin in skeletal muscle increased circulating myonectin levels and attenuated cardiac injury after ischemia-reperfusion. In addition, systemic administration of myonectin protein to WT mice reduced infarct size after myocardial ischemia-reperfusion. Myonectin expression is hardly detected in the heart. These findings indicate that an increase in skeletal muscle-derived myonectin contributes to improvement of cardiac injury after ischemia-reperfusion in an endocrine manner.

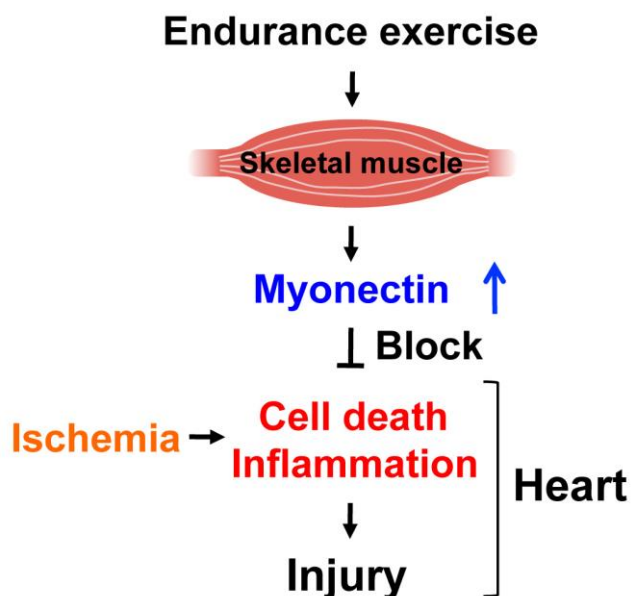
In vitro studies demonstrated that myonectin suppressed apoptosis of cardiac myocytes under conditions of hypoxia/reoxygenation. Myonectin also attenuated endotoxin-stimulated expression of inflammatory mediators in cultured macrophages. Furthermore, myonectin promotes sphingosine-1-phosphate-dependent signaling pathways, thereby leading to reduction of cardiomyocyte apoptosis and macrophage inflammation.

Our data indicate that myonectin functions as an endurance exercise-induced myokine which ameliorates acute myocardial ischemic injury by suppressing apoptosis and inflammation in the heart, suggesting that myonectin can partly mediate the cardiovascular benefits of endurance exercise.

Research Summary and Future Perspective

We found that myonectin is a cardioprotective hormone, which partly mediates the cardiovascular benefits of endurance exercise. Myonectin can represent a novel target molecule for prevention or

treatment of cardiac diseases that are improved by physical exercise.



Cardioprotection by myonectin

Publication

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Myonectin is an exercise-induced myokine that protects the heart from ischemia-reperfusion injury

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