ピオグリタゾンによるウサギ静脈グラフトモデル内膜肥厚抑制効果の検討

森﨑, 浩一
九州大学大学院医学系学府

https://doi.org/10.15017/21734

出版情報：九州大学, 2011, 博士（医学）, 課程博士
バージョン：
権利関係：

Pioglitazone prevents intimal hyperplasia in experimental rabbit vein graft

Koichi Morisaki, MD[1], Rei Shibata, MD, PhD[2], Noriyuki Ouchi, MD, PhD[3], Yoshihiko Maehara, MD, PhD[4], Toyoaki Murohara, MD, PhD[2] and Kimihiro Komori, MD, PhD[1]

[1]Division of Vascular Surgery, Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan
[2]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[3]Molecular Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[4]Department of Surgery and Science, Kyushu University, Graduate School of Medical Science, Fukuoka, Japan

Background: Intimal hyperplasia is a major cause of obstacle to patency after vein grafting. Several clinical trials revealed that peroxisome proliferators-activated receptor-γ ligand, pioglitazone exerts beneficial actions on cardiovascular complications. Here, we investigated whether pioglitazone modulates intimal hyperplasia in an experimental rabbit autologous vein graft.
Methods: Male Japanese white rabbits were randomly divided into two groups and were treated with or without pioglitazone as food admixture at a concentration of 0.01%. One week later, each group underwent reversed autologous vein bypass grafting of the right common carotid artery using ipsilateral external jugular vein. Pioglitazone therapy was continued after surgery and until the time harvest. Intimal hyperplasia of the grafted vein was assessed at 28 days after surgery. Two weeks after implantation, proliferative cells in neointima were identified by immunohistochemical staining with Ki-67 monoclonal antibody. To determine apoptotic cells, we also performed terminal transferase-mediated deoxyuride-5'-triphosphate nick-end labeling (TUNEL) staining. Blood samples were collected at 28 days after implantation for measuring metabolic parameters such as plasma glucose and total cholesterol. Adiponectin levels were determined by western blotting analysis. Finally, we assessed adiponectin-related signaling pathway, AMP-activated protein kinase (AMPK) and extracellular signal-regulated kinase (ERK) in the grafted vein by Western blot analysis.
Results: Treatment with pioglitazone markedly inhibited intimal hyperplasia of carotid interposition-reversed jugular vein grafts (pioglitazone treated group, 0.54±0.04 mm^2 vs

control group, 0.93±0.04 mm^2; n = 7; P＜ .01). Pioglitazone treatment reduced the number of Ki-67 positive proliferating cells in the neointima of the vein graft at 14 days after implantation (pioglitazone treated group, 4.1±1.1 % vs control group, 16.8±1.7 %; p＜ .05), whereas the frequency of TUNEL positive apoptotic cells was enhanced by pioglitazone (pioglitazone treated group, 3.5±0.5 % vs control group, 1.2±0.1 %; p ＜ .05). Treatment with pioglitazone also increased plasma levels of a vascular protective hormone adiponectin. Furthermore, pioglitazone treatment led to an increase in phosphorylation of AMPK and a decrease in phosphorylation of ERK in the grafted vein.

Conclusions: Pioglitazone attenuates intimal hyperplasia of the vein graft after autologous bypass grafting by its ability to suppress cell proliferation and enhance apoptosis. Pioglitazone could represent a therapeutic target for the prevention of graft failure after bypass grafting.