Rosiglitazone reduces ischaemia-reperfusion injury in patients with the metabolic syndrome

Alexander J. Rennings1*, Patrick Meijer2, Dominique J. van Uden1, Cees J. Tack1, Paul Smits1,3, Otto C. Boerman4, Wim J. Oyen4, and Gerard A. Rongen1,3

1Department of Pharmacology-Toxicology, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands; 2Department of Anaesthesiology, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands; and 3Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands; 4Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands 

*a Corresponding author. Tel: +31 24 361 4597, Fax: +31 24 361 4214, Email: a.rennings@pharmtox.umcn.nl

In animals, thiazolidinediones reduce ischaemia-reperfusion injury. A clinical meta-analysis raised suspicion that rosiglitazone increases the incidence of myocardial infarction (Nissen et al., N Engl J Med 2007;356:2457–2471). However, human data on a possible benefit on infarct size (i.e. ischaemia-reperfusion injury) are not available. Therefore, we investigated the effect of rosiglitazone on ischaemia-reperfusion injury in 10 insulin resistant participants without hyperglycaemia. We used a thoroughly validated human in vivo model to quantify ischaemia-reperfusion injury in skeletal muscle by annexin-A5-scintigraphy (Rorgen et al., Circulation 2005;111:173–178). At the end of each treatment period (rosiglitazone 4 mg b.d. vs. placebo), the participants were subjected to 10 min of forearm ischaemia, combined with standardized intermittent handgripping. At reperfusion, 500 MBq 99mTc-annexin-A5 was administered intravenously. Annexin-uptake (counts per pixel) was measured in thenar muscle 1 h post-reperfusion using a gamma camera. Ischaemia-reperfusion injury was quantified as the percentage difference in uptake between experimental and control side (annexin-targeting). Rosiglitazone reduced annexin-targeting from 8.4% (median; range 0.6–49%) to 4.7% (0.7–20%) (P = 0.037). We present the first human in vivo data on the beneficial effects of rosiglitazone on ischaemia-reperfusion injury. This observation puts the disputed elevation in myocardial ischaemic events during rosiglitazone treatment in perspective.

Panel A. Study design.

Panel B. Individual plots of the effects of rosiglitazone on 99mTc-annexin-targeting in insulin resistant subjects.

Panel C. Typical 99mTc-annexin-uptake one hour after reperfusion at the end of the placebo period. Left: control hand; right: post-ischaemic hand. Counts increase from blue to yellow.

Panel D. Same patient, but at the end of the rosiglitazone treatment period.