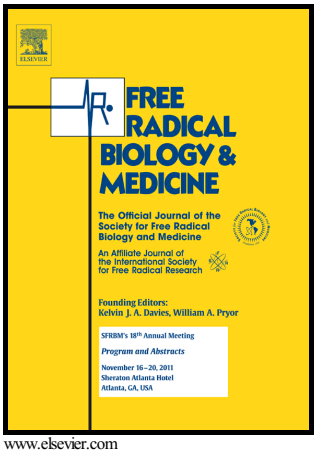

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Advanced glycation end products receptor RAGE controls myocardial dysfunction and oxidative stress in high-fat fed mice by sustaining mitochondrial dynamics and autophagy-lysosome pathway

Yu Yichi [1,21], Wang Lei [1,2,1], Delguste Florian [1], Durand Arthur [1,3], Guilbaud Axel [1], Rousselin Clementine [1,3], Schmidt Ann Marie [4], Tessier Frédéric [1], Boulanger Eric [1,3], Neviere Remi [1,5]

[1]INSERM U995, LIRIC /Team "Glycation: from inflammation to aging", Lille University, France
[2]School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[3]University Hospital CHU of Lille, F-59000 Lille, France
[4]Diabetes Research Center, Department of Medicine, NYU Langone Medical Center, New York, NY, USA
[5]University Hospital CHU of Martinique, University of Antilles, Fort de France, F-97200, France
*Corresponding author. University Hospital CHU of Martinique, University of Antilles, Fort de France, F-97200, France. Tel.: +596 696 19 44 99. remi.neviere@chu-martinique.fr

ABSTRACT

Oxidative stress and mitochondrial dysfunction are recognized as major contributors of cardiovascular damage in diabetes and high fat diet (HFD) fed mice. Blockade of receptor for advanced glycation end products (RAGE) attenuates vascular oxidative stress and development of atherosclerosis. We tested whether HFD-induced myocardial dysfunction would be reversed in RAGE deficiency mice, in association with changes in oxidative stress damage, mitochondrial respiration, mitochondrial fission and autophagy-lysosomal pathway. Cardiac antioxidant capacity was upregulated in $RAGE^{-/-}$ mice under normal diet as evidenced by increased superoxide dismutase and sirtuin mRNA expressions. Mitochondrial fragmentation and mitochondrial fission protein Drp1 and Fis1 expressions were increased in $RAGE^{-/-}$ mice. Autophagy-related protein expressions and cathepsin-L activity were increased in $RAGE^{-/-}$ mice suggesting sustained autophagy-lysosomal flux. HFD induced mitochondrial respiration defects, cardiac contractile dysfunction, disrupted mitochondrial dynamics and autophagy inhibition, which were partially prevented in $RAGE^{-/-}$ mice. Our results suggest that cardioprotection against HFD in $RAGE^{-/-}$ mice include reactivation of autophagy, as inhibition of autophagic flux by chloroquine fully abrogated beneficial myocardial effects and its

[1] Equally contribute to this work