

The AGE-breaker ALT-711 restores high blood flow-dependent remodeling in mesenteric resistance arteries in a rat model of type 2 diabetes

Submitted by Emmanuel Lemoine on Tue, 02/24/2015 - 16:14

Titre	The AGE-breaker ALT-711 restores high blood flow-dependent remodeling in mesenteric resistance arteries in a rat model of type 2 diabetes
Type de publication	Article de revue
Auteur	Freidja, M. L [1], Tarhouni, K. [2], Toutain, Bertrand [3], Fassot, C�line [4], Loufrani, Laurent [5], Henrion, Daniel [6]
Editeur	American Diabetes Association
Type	Article scientifique dans une revue � comit� de lecture
Ann�e	2012
Langue	Anglais
Date	2012
Num�ro	6
Pagination	1562 - 72
Volume	61
Titre de la revue	Diabetes
ISSN	1939-327X
Mots-cl�s	Animals [7], Blood Pressure/drug effects/physiology [8], Diabetes Mellitus, Type 2/drug therapy/metabolism/physiopathology [9], Endothelium, Vascular/drug effects/metabolism/physiopathology [10], Glycosylation End Products, Advanced/metabolism [11], Male [12], Mesenteric Arteries/drug effects/metabolism/physiopathology [13], Rats [14], Rats, Zucker [15], Thiazoles/pharmacology/therapeutic use [16], Vascular Resistance/drug effects/physiology [17], Vasodilation/drug effects/physiology [18]

Résumé en anglais	Flow-mediated remodeling of resistance arteries is essential for revascularization in ischemic diseases, but this is impaired in diabetes. We hypothesized that breaking advanced glycation end product (AGE) cross-links could improve remodeling in mesenteric resistance arteries in Zucker diabetic fatty (ZDF) rats compared with lean Zucker (LZ) rats. Arteries, exposed to high (HF) or normal (NF) blood flow after alternate arterial ligation in vivo, were collected after 2 weeks. In LZ rats, HF artery diameter was larger than for NF vessels, but this was not the case in ZDF rats. Endothelium-mediated dilation in ZDF rats, which was lower than in LZ rats, was further decreased in HF arteries. Treatment of rats with the AGE-breaker 4,5-dimethyl-3-phenacylthiazolium chloride (ALT-711) (3 mg/kg/day; 3 weeks) reversed diabetes-induced impairment of HF-dependent remodeling. ALT-711 also improved endothelium nitric oxide-dependent relaxation in mesenteric resistance arteries. Reactive oxygen species reduction restored relaxation in ZDF rats but not in LZ or ALT-711-treated rats. AGEs were reduced in ALT-711-treated ZDF rats compared with ZDF rats. Metalloproteinase activity, necessary for HF-dependent remodeling, was reduced in ZDF rats compared with LZ rats and restored by ALT-711. Thus, targeting AGE cross-links may provide a therapeutic potential for overcoming microvascular complications in ischemic disorders occurring in diabetes.
URL de la notice	http://okina.univ-angers.fr/publications/ua8432 [19]
DOI	10.2337/db11-0750 [20]
Lien vers le document	http://dx.doi.org/10.2337/db11-0750 [20]
Titre abrégé	Diabetes

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- [20] <http://dx.doi.org/10.2337/db11-0750>

Publié sur *Okina* (<http://okina.univ-angers.fr>)