Pro-Angiogenic Effects of Low Dose Ethoxidine in a Murine Model of Ischemic Hindlimb: Correlation between Ethoxidine Levels and Increased Activation of the Nitric Oxide Pathway

Titre	Pro-Angiogenic Effects of Low Dose Ethoxidine in a Murine Model of Ischemic Hindlimb: Correlation between Ethoxidine Levels and Increased Activation of the Nitric Oxide Pathway
Type de publication	Article de revue
Auteur	Clere, Nicolas [1], To, Kim Hung Thien [2], Legeay, Samuel [3], Bertrand, Samuel [4], Helesbeux, Jean-Jacques [5], Duval, Olivier [6], Faure, Sébastien [7]
Pays	Suisse
Editeur	MDPI
Ville	Bâle
Type	Article scientifique dans une revue à comité de lecture
Année	2017
Langue	Anglais
Date	12 Avril 2017
Numéro	4
Pagination	627
Volume	22
Titre de la revue	Molecules
ISSN	1420-3049
Mots-clés	Angiogenesis [8], Ethoxidine [9], Ischemia [10], neovascularization [11], Nitric oxide [12], VEGF [13]

Résumé en anglais	Ethoxidine, a benzo[c]phenanthridine derivative, has been identified as a potent inhibitor of topoisomerase I in cancer cell lines. Our group has reported paradoxical properties of ethoxidine in cellular processes leading to angiogenesis on endothelial cells. Because low concentration ethoxidine is able to favor angiogenesis, the present study aimed to investigate the ability of 10−9 M ethoxidine to modulate neovascularization in a model of mouse hindlimb ischemia. After inducing unilateral hindlimb ischemia, mice were treated for 21 days with glucose 5% or with ethoxidine, to reach plasma concentrations equivalent to 10–9 M. Laser Doppler analysis showed that recovery of blood flow was 1.5 fold higher in ethoxidine-treated mice in comparison with control mice. Furthermore, CD31 staining and angiographic studies confirmed an increase of vascular density in ethoxidine-treated mice. This ethoxidine-induced recovery was associated with an increase of NO production through an enhancement of eNOS phosphorylation on its activator site in skeletal muscle from ischemic hindlimb. Moreover, real-time RT-PCR and western blots have highlighted that ethoxidine has pro-angiogenic properties by inducing a significant enhancement in vegf transcripts and VEGF expression, respectively. These findings suggest that ethoxidine could contribute to favor neovascularization after an ischemic injury by promoting the NO pathway and VEGF expression.
URL de la notice	http://okina.univ-angers.fr/publications/ua15866 [14]
DOI	10.3390/molecules22040627 [15]
Lien vers le document	http://www.mdpi.com/1420-3049/22/4/627 [16]
Titre abrégé	Molecules

Liens

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