Investigating the anti-atherosclerotic effects of a cyclic azapeptide, MPE-298, ligand of CD36/SR-B2 in hypercholesterolemic apolipoprotein E-deficient mice

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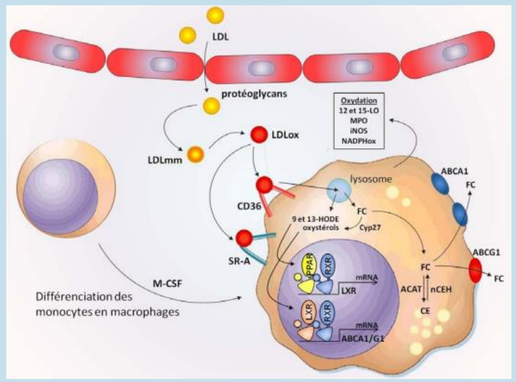
Introduction

Atherosclerosis, the accumulation of lipids in the intima of arteries which reduces vessel lumen, is the most important cause of cardiac ischemic diseases.

The scavenger receptor CD36 (SR-B2), expressed by macrophages, is one of the main receptors implicated in the internalisation and metabolism of oxidized low density lipoproteins (oxLDL). Dysregulation of this function induces an increase of atherosclerotic plaques and inflammation.

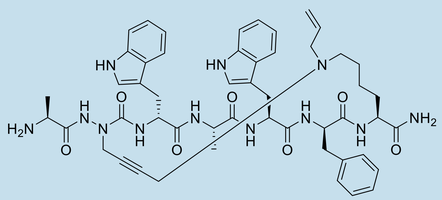


Régulation du métabolisme et du transport des lipides dans les macrophages: potentiel anti-athérosclérotique des ligands du CD36
Thèse de Kim Bujold, Université de Montréal, 2012

Hypothesis and objectives

MPE-298, a selective ligand of CD36 derived from the growth hormone-releasing peptide-6 (GHRP-6) will reduce atherosclerotic lesions at the level of the aortic arch in a murine model of atherosclerosis (apolipoprotein E deficient or ApoE-/- mice).

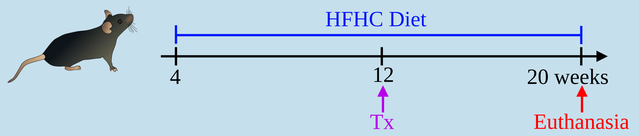
The objective of this study was to characterize the antiatherosclerotic effects of MPE-298 in ApoE-/- mice.



Methods

Male ApoE-/- mice were fed with a lipid and cholesterol rich diet (HFHC, cholesterol at 1.25%) from 4 to 20 weeks. Food consumption and weight were measured each week.

Methods

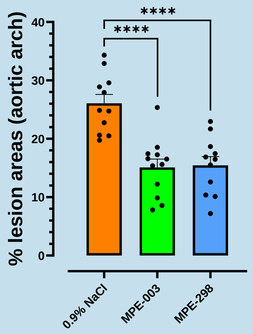


Treatment (Tx) by MPE-298 (300 nmol/Kg) or vehicle (0,9% NaCl) were given subcutaneously every day during 8 weeks, 12 to 20 weeks.

- Euthanasia (by isoflurane and exsanguination)
- Tissues collected :
  - Aortas (dissected et colored with Oil-Red-O);
  - Blood (plasma conserved for analysis).

Results

MPE-003, a linear azapeptide with known antiatherosclerotic properties was used as a positive control (Frégeau et al., Atherosclerosis, 2020).



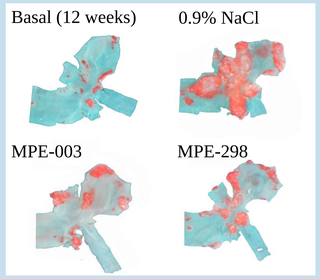
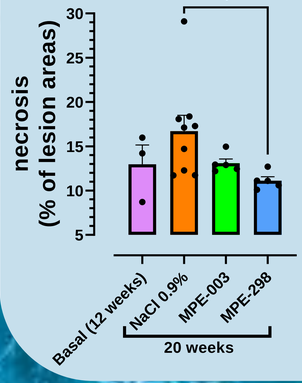


Figure 1. MPE-298 and MPE-003 reduced aortic arch lesion areas by 41% and 42% compared to vehicle, respectively.



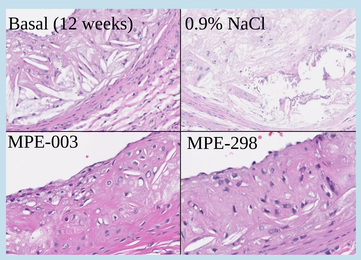


Figure 2. MPE-298 reduced aortic sinus necrosis areas by 33%.

Results

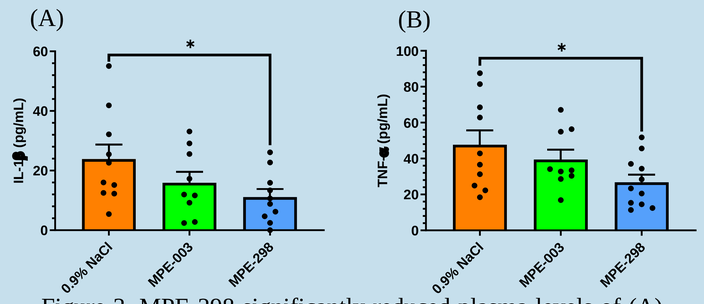


Figure 3. MPE-298 significantly reduced plasma levels of (A) IL-1β and (B) TNF-α.

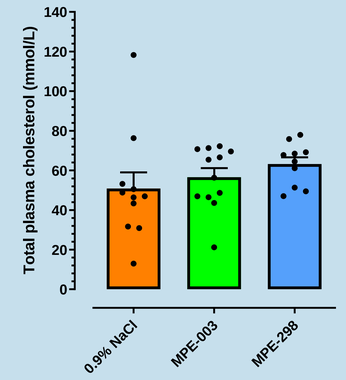


Figure 4. Azapeptides do not modulate plasma cholesterol levels.

Conclusion and perspectives

MPE-298 reduces atherosclerotic lesion progression. These effects are associated with a reduction of necrosis areas, which could indicate an increase in lesion stability. In addition, reduced plasma levels of cytokines IL-1β and TNF-α, may indicate an anti-inflammatory effect of the azapeptide. Theses effects appear to be independent of plasma cholesterol levels.

Future studies will evaluate the cellular mechanisms involved in the anti-atherosclerotic effects of MPE-298 azapeptide.

Acknowledgements