THERAPEUTIC ACTIONS OF PRO-RESOLVING LIPOXIN A4 MIMETICS AGAINST ATHEROSCLEROSIS

Muthukumar Mohan ¹, Anna M.D. Watson ¹, Karly C. Sourris ¹, Eoin P. Brennan², Catherine Godson², Mark E. Cooper ¹, Phillip Kantharidis ¹.

¹ JDRF Danielle Alberti Memorial Centre for Diabetes Complications, Department of Diabetes, Monash University, Melbourne, Australia; ² UCD School of Medicine and Medical Sciences, UCD Conway Institute of Biomolecular & Biomedical Research, Dublin, Ireland.

INTRODUCTION: Patients with diabetes are at high risk of developing cardiovascular complications, including CAD and stroke, due to chronic inflammation leading to the build-up of atherosclerotic plaque in the arterial wall. Recent insights into the use of pro-resolving molecules, such as Lipoxin A₄ (LXA₄), has highlighted the novel therapeutic potential of Lipoxins against atherosclerosis. Here, we investigated the effectiveness of number of LXA₄ mimetics in attenuating diabetes-associated atherosclerosis (DAA).

Fig 1: Study design for 10-week prevention

Fig 3: Metabolic data of 10-week prevention study

		Body weight	Blood Pressure	Glucose (mmol/L)	Glycated HbA1c	
					%	mmol/mol
Control	Vehicle	32 ± 0.6	96 ± 3.8	11.5 ± 1.0	4.4 ± 0.2	24.4 ± 2.1
	LXA ₄	30 ± 0.6	104 ± 3.8	11.0 ± 0.8	4.2 ± 0.1	22.4 ± 1.0
	CT4-43	30 ± 0.5	87 ± 3.1	10.2 ± 2.8	4.3 ± 0.1	23.3 ± 1.2
	KG522	31 ± 0.5	99 ± 3.2	10.3 ± 0.8	4.1 ± 0.1	21.1 ± 0.8
Diabetes	Vehicle	25 ± 0.8 ††††	100 ± 3.9	27.0 ± 4.8 ††	11.2 ± 0.4	98.8 ± 4.4 ††††
	LXA ₄	26 ± 1.3 †	98 ± 5.5	30.2 ± 1.6 †††	11.0 ± 0.9	96.8 ± 9.7 ††††
	CT4-43	26 ± 0.8 †	101 ± 9.6	27.5 ± 3.3 ††	11.1 ± 1.0	98.1 ± 10.6 ††††
	KG522	23 ± 0.9 ††††	93 ± 3.8	30.5 ± 2.0 †††	9.6 ± 0.7	81.8 ± 7.9 ††††

Fig 4: qPCR results from D-HAoSMC cells treated with TNFα (2ng) and LXs after 24hr

CONCLUSION: To date, our findings reveal novel pro-resolving effects of LXA₄ mimetics against inflammation induced-atherosclerosis, reversing inflammatory processes and plaque deposition. These results support our hypothesis that LXs can be used as a novel approach for the treatment of DAA.

AIM: The aim of this study was to investigate the therapeutic potential of LXA₄ and two LXA₄ mimetics against DAA in diabetic ApoE^{-/-} mice

METHODS: ApoE^{-/-} mice were rendered diabetic by five-daily intraperitoneal (IP) injections of streptozotocin (55mg/kg); control mice received citrate buffer. LXA₄ (5µg/kg), and two LXA₄ mimetics namely - CT4-43 (1.7µg/kg) and KG522 (3µg/kg) were administered twice weekly for 10-weeks via IP injection in control and diabetic mice. At end-point, mice were culled and aortae collected and analysed for plaque deposition, gene expression, immunohistochemistry and histology.

RESULTS:

Fig 2: Total plaque deposition and plaque deposition in arch of the aorta from 10-week prevention model

Acknowledgements: This work is supported by the NHMRC Research project grant.

Copyright © 2019 Muthukumar Mohan
Muthukumar.mohan@monash.edu