Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol16Issue1abst067P.pdf

Simvastatin reduces interleukin-1 beta secretion from peripheral blood mononuclear cells when treated wiht cholesterol crystals

M. Lucitt[1], N. Gangadharan[1], P. Kavanagh[1], P. Walsh[2], L. Hemeryck[1], J. Kieran[1], M. Barry[1]. [1]Pharmacology and Therapeutics, Trinity College Dublin, Dublin, IRELAND, [2]Clinical Medicine, Trinity College Dublin, Dublin, IRELAND.

Introduction The NLRP3 inflammasome is activated in response to endogenous danger signals such as cholesterol crystals (CC) in innate immune cells and directs inflammatory responses through regulating interleukin-1 beta (IL-1β) release (1). Considerable evidence now clearly implicates a central role for IL-1β in the pathogenesis of atherosclerosis (1) revealing its potential as a novel therapeutic target. Statins are known to have anti-inflammatory effects (2). However, the specific mechanisms and how these may affect disease pathogenesis remain to be established.

Method We used a model of NLRP3 inflammasome activation to trigger maturation of IL-1β in PBMCs isolated from whole blood (1) to test the anti-inflammatory effects of simvastatin. PBMCs were isolated from healthy donors and treated in vitro with simvastatin (100uM) or from hyperlipidemic patients at baseline, and following 8 weeks simvastatin (10-20mg) daily treatment. PBMCs were then stimulated with LPS (100ng/ml) for 3 hrs to upregulate pro IL-Iβ expression, followed by CC (1mg/ml) stimulation for 24hrs to activate the NLRP3 inflammasone complex involved in processing IL-1β to its mature form. IL-Iβ levels in the supernatants form PBMCs was measured by ELISA. All experiments carried out were approved by the Medical Research Ethics Committees at St James Hospital/AMNCH, Dublin 8, Ireland and comply fully with the Declaration of Helsinki.

Results: Patients (n=9) taking simvastatin (10-20mg daily) over a peroid of 8 weeks exhibited reduced LDL cholesterol (4.87 ± 0.76 mmol/L) pre vs (3.78 ± 0.67 mmol/L) post. Simvastatin treatment also resulted in reduced levels of IL-1β secretion by PBMCs, upon stimulation with LPS and CC, when compared to levels detected prior to the initiation of treatment (5.27 ± 0.6 ng/ml) pre vs (4.27 ± 0.5 ng/ml) post. Similarly, i*n vitro* treatment of PBMCs with simvastatin (100uM) also resulted in reduced IL-1β secretion upon activation with LPS and CC (2.37± 0.17 ng/ml) controls vs (0.64 ± 0.06 ng/ml) simvastatin. *Values presented are mean ± sem*

Conclusions As part of our preliminary investigations, we have demonstrated that CC induced IL-1β release by PBMCs from hyperlipidemic patients, and that levels of IL-1β released are reduced in these patients after treatment with simvastatin. These data identify a previously unappreciated beneficial role for statin therapy in atherosclerotic patients.

References

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