Medina *et al.: Intrinsic Activity*, 2015; **3**(Suppl. 2):A1.17
http://www.intrinsicactivity.org/2015/3/S2/A1.17
published online: 9 Septembe 2015

INTRINSIC ACTIVITY

21st Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the British Pharmacological Society and the Pharmacological Societies of Croatia, Serbia and Slovenia

Graz, 16–18 September 2015

MEETING ABSTRACT

A1.17

Ets-2, a possible marker of early instability in coronary artery bypass grafting patients: modulation by drugs

Úrsula MEDINA[1], Marta RAMAJO[1], Mónica GARCÍA BOUZA[2], Fernando REGUILLO[2], Manuel CARNERO[2] and Teresa TEJERINA[1,*]

[1]Department of Pharmacology, School of Medicine, Universidad Complutense de Madrid, Spain; [2]Cardicac Surgery Service, Hospital Clínico San Carlos, Madrid, Spain

Background: Endothelial progenitor cells (EPCs) play a key role in endothelial repair processes. It is well known that the functionality of the EPCs is poor in patients with diabetes mellitus type 2 (DM2) and cardiovascular disease (CVD), although the exact mechanism of dysfunction is still uncertain. Several studies have pointed out the importance of adequate therapy (*e.g.* therapy with EPCs) for endothelial repair, helping to reduce the alterations in the processes of re-endothelization in patients with DM2 and CVD and therefore decrease the occurrence of CVD. Recently, the SDF-1 axis and the CXCR4 co-receptor have become a key element in the study of CVD. Moreover, it has been hypothesized that members of the E26 family of transcription factors are involved in the development of CVD, and in patients with DM2, the specific alteration of the transcription factor Ets-2 could contribute to the dysfunction of the EPCs. Our main objective was (i) to determine whether the degree of expression of Ets-2–SDF-1α/CXCR4 is capable of predicting the release of circulating EPCs, (ii) to relate the data found with clinical and laboratory parameters of patients undergoing coronary artery bypass grafting (CABG), and (iii) to study their modulation by DPP4 inhibitor drugs (sitagliptin).

Methods: Ninety CABG patients were divided into diabetic and non-diabetic patients (NDM). Peripheral mononuclear cells were obtained by Ficoll-Hypaque density gradient centrifugation. Expression of Ets-2, CXCR4, and SDF-1 were measured by western blotting. The effects of sitagliptin on EPCs in culture were measured by western blotting, ELISA and immunofluorescence.

Results: In patients with DM2, release of EPCs, determined by levels of SDF-1α, is a late effect due to the high levels of glucose and low levels of HDL, but this effect decreases in patients treated with insulin. In DM2 patients a low expression in the SDF-1/CXCR4 axis was observed in comparison to NDM patients (NDM: 3.20 ± 2.3 *vs.* DM2: 1.41 ± 1.4; NDM: 1.32 ± 1.0 *vs.* DM2: 1.08 ± 0.9), which was associated with low levels of expression of Ets-2 (NDM: 1.60 ± 1.5 *vs.* DM2: 1.17 ± 1.0). However, an increase in expression of Ets-2 was observed in patients without cardiovascular risk factor (2.12 ± 1.5), associated with early stages of cardiovascular instability, while the expression was decreased in patients with longer evolution of CVD. In EPCs in culture, sitagliptin improved cell morphology and increased the expression of SDF-1α and CXCR4 at 24 hours; this effect did not depend on stimulus by apoptotic bodies.

Discussion: In patients with DM2, release of EPCs is a result of the SDF-1α axis and the CXCR4 co-receptor. Poor functionality of circulating EPCs is associated with decreased expression of the transcription factor Ets-2 in advanced stages of CVD in patients with DM2. Ets-2 could be an early marker of cardiovascular instability associated with states of hyperlipidemia. Therapy with sitagliptin in EPCs in culture could help to reverse the poor functionality of the EPCs, especially in patients with DM2.

Acknowledgements: This work was supported by FIS PI12/00590 (plan estatal I+D+I 2013–2016).

*Corresponding author e-mail: *teje@ucm.es*