VASOCONSTRICTION INHIBITING FACTOR: AN ENDOGENOUS NEW CALCIMIMETIC OF THE CALCIUM-SENSING RECEPTOR THAT INHIBITS VASCULAR CALCIFICATION

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Introduction

Patients with chronic kidney disease (CKD), have an increased risk of cardiovascular disease due to the massively accelerated calcification they develop [1]. Vascular calcification is a highly regulated process mediated by different inducers and inhibitors [2]. The peptide 'vasoconstriction inhibiting factor' (VIF) was recently discovered and described as an inhibitor of the angiotensin II-induced vasoconstriction [3]. Angiotensin II inhibits calcium deposition [4], but VIF effect on vascular calcification is still unknown.

Methods

The effect of VIF was analysed *in vitro* in human aortic smooth muscle cells (hAoSMCs) and *ex vivo* in rat aortic rings, both cultivated under high phosphate concentrations. VIF was also studied *in vivo* in rats treated with vitamin D and nicotine (VDN) as calcification model. HEK-293 cells overexpressing calcium-sensing receptor were used for the study of VIF receptor.

Results

VIF inhibits calcium deposition in all the models studied. Furthermore, in hAoSMC VIF reduces the production of ROS and the initiation of diverse cascades in the cells, like activation of inflammatory cytokines and MAPK kinases, which in turn trigger the expression of various genes involved in the development of vascular calcification. Furthermore, in presence of VIF the population of apoptotic cells, directly linked to vascular calcification, is decreased. Calcium-sensing receptor (CaSR) has been found as VIF binding partner. The production of the calcification inhibitor, carboxy-Matrix Gla Proteins (cMGP) is increased when VIF is given to hAoSMCs and VDN rats. Moreover, CKD patients with extensive calcification show negative correlation between calcification score and VIF concentration

Discussion

VIF is a new potent endogenous inhibitor of vascular calcification that acts as a calcimimetic of the CaSR, leading to an increase production of cMGP. This finding represents a basis for a new target for the prevention and therapy of patients with increased vascular calcification and shows an encouraging perspective for the future.

Figure

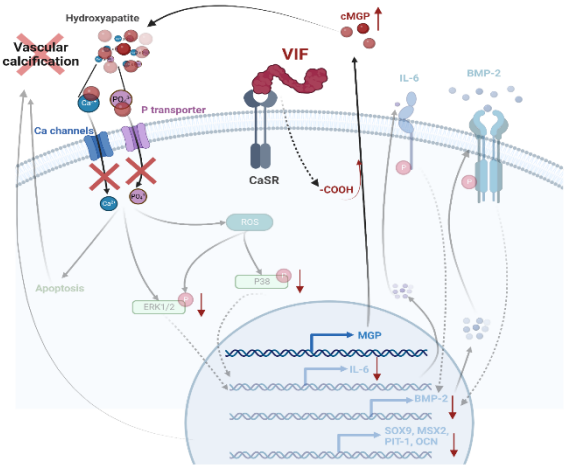

Figure 1: The VIF peptide mechanism to inhibit vascular calcification: When the VIF peptide is added to calcified environment, it acts as a calcimimetic of CaSR and increases cMGP production, which after binding to the hydroxyapatite crystal, reduce calcium influx andt inhibits the activation of calcification pathways (ROS production, kinase activation secretion of inflammatory cytokines, activation of calcification-related genes and apoptosis).

References

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