Gliptins modulate vascular tone through L-arginine/eNOS Pathway

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Dipetidil-peptidase-IV (DPP-IV) represent a class of endogenous enzymes involved in the degradation of incretin hormones, such as Glucagon like peptide 1 (GLP-1) and Glucose dependent insulinotropic polypeptide (GIP) (Zhong et al., 2013). Incretin system is involved in the regulation of postprandial glycemic control and satiety. In response to food intake, GLP-1 and GIP, released by the gut, induce insulin synthesis and secretion, inhibit glucagon release and reduce glucose production by the liver, lowering glycemia. The ipoglycaemic action of GLP-1 is transient, due to its short life-time. DPP-IV inhibitors, often referred to as *gliptins*, represents a new approach in the treatment of type 2 diabetes mellitus (T2DM) by virtue of its effects on prolonging the half-life of incretins. At the present stage, five different inhibitors has been approved for the treatment of T2DM *(*sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin). Recent studies suggests that gliptins, beyond the well-known antihyperglycemic and pancreatic islet protective effects, exert a beneficial pleiotropic action on heart and vessels (Ye et al., 2010; Chinda et al., 2013). Furthermore, it has been demonstrated that the gliptins improve vascular endothelial dysfunction that is significantly impaired in diabetic patients. The mechanisms through which gliptins exert their vascular effect are still controversial so the aim of this study is to evaluate the molecular mechanisms involved in beneficial action of gliptins, in particular of Linagliptin and Sitagliptin. To pursue this goal we performed *in vitro* experiments on isolated aortic and carotid rings harvested from CD-1 mice. Cumulative concentration response curves of Linagliptin and Sitagliptin (100nM-30μM) have been evaluated. In physiological conditions, Linagliptin induced vasodilatation that reaches a maximum effect (Emax) of 89.4 ± 2.58% and 89.7 ± 5.64% in aorta and carotid rings respectively at the concentration of 30 μM. Also Sitagliptin induces vasodilatation that achieves an Emax= 49.0 ± 11.3% in aorta and 21 ± 4.48% in carotid at the maximal concentration used (30 μM). However the relaxing effect of Sitagliptin was lower compared to Linagliptin. Endothelial removal significantly reduces Linagliptin-induced vasodilation both in aorta and carotid rings. Moreover, incubation with L-NIO, an eNOS inhibitor, or with ODQ, a sGC inhibitor, significantly reduces Linagliptin-induced vasodilation in both tissues. Recent literature reported that the relaxation induced by gliptins is partially mediated by the interaction between GLP-1 and its receptor (GLP-1R) (Liu et al., 2012). To assess if the vasodilating effect of Linagliptin is due to GLP-1R activation, we performed a set of experiments on GLP-1R$^{-/-}$ mice. In aortic rings harvested from these animals, Linagliptin still shows its vasorelaxing property and the vasodilating effect is inhibited by L-NIO or ODQ treatment as well. Our results suggest that Linagliptin induces vasodilatation on vascular tissues such as mouse aorta and carotid. Moreover its relaxing activity is partially due to the activation of eNOS/NO pathway and it is independent on GLP-1/ GLP-1R pathway.

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Chinda et al., (2013) *Int J Cardiol* 167(2): 451-7.
Liu et al., (2012) *Hypertension* 60(3): 833-41.