Effect of *aliskiren* on (pro)renin receptor expression and activity: in vitro determination of TGF-β, PAI-1 and type I collagen expression andsmooth muscle cell migration

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The recent discovery of a specific receptor for renin/prorenin (PRR) has added new interest to the pharmacological actions of aliskiren, the first direct renin inhibitor. In the present study we investigated the effect of aliskiren on PRR expression and activity in cultured human smooth muscle cells (SMCs). Co-incubation of SMCs with angiotensinogen (ANG) (1.5×10^{-7} M) and prorenin (10^{-8}–10^{-7} M) resulted in an efficient production of angiotensin I, almost completely inhibited by 10^{-5} M aliskiren (-86.0 ± 14.0%). A 24 h incubation with aliskiren (10^{-6}–10^{-5} M) resulted in a concentration-dependent reduction of PRR mRNA levels (IC_{50} 4.6×10^{-6} M), total and the cell surface expression of PRR (IC_{50} 9.1×10^{-6} M). The lower levels of PRR were associated with a reduced expression of TGF-β, PAI-1 and type I collagen mRNA. The effect of prorenin on SMC migration was also investigated. Prorenin induced SMC migration in a dose-dependent manner, as assessed by Boyden chamber chemotaxis assay. The knockdown of PRR by small interfering RNA completely inhibited the migratory response to prorenin, demonstrating that the chemotactic action of prorenin is mediated by the PRR. Prorenin increased the intracellular levels of both RhoA-GTP (+47.8%) and Rac1-GTP (+36.7%) through PRR. A 24 h incubation with aliskiren (10^{-5} M) determined a significant inhibition of SMC migration induced by prorenin (-35.7±9.7%; $P<0.05$) while no significant effect was observed when PDGF-BB was utilized as chemotactic agent. Aliskiren (10^{-5}M) also blunted the induction of Rac1-GTP levels in response to prorenin without affecting the RhoA activity. In conclusion aliskiren elicits a direct pharmacological action on PRR expression and its signaling pathway in SMCs, affecting gene expression of TGF-β, PAI-1 and type I collagen and reducing the chemotactic action of prorenin on SMCs. These results, although obtained from in vitro analysis, may help to better define the pharmacological properties of aliskiren on atherosclerosis.

The present work was supported by a grant from Novartis Farma S.p.A., Origgio, Italy.