Shear Stress-Induced AT1 Receptor Activation Independent of the Ligand can be Antagonized by Receptor Blockers

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Although humoral factors contribute to the development of cardiac or vascular remodeling during the increase in haemodynamic load, a large body of evidence indicates that mechanical stress can also play a role in this response. Mechanical stretch can activate Ang II AT1 receptor (AT1) independently of its ligand, and this activation can be blocked by an inverse agonist effect from AT1 blockers (ARBs) of the AT1. In the present study, we tested the hypothesis that AT1 is activated by shear stress (SS) and verified whether this response is dependent of the natural ligand and the ability of ARBs to modify it. Using western blotting technique we observed that AT1-overexpressed CHO cells submitted to SS (15 dynas/cm^2, 10 min) can activated ERK½ (287±16%) while the response in wild-type CHO cells was virtually absent (26±8%). The SS-induced response is dependent on increase in intracellular Ca2+ since BAPTA-AM, a intracellular calcium chelator, almost completely abrogated the ERK½ activation by SS. The investigation of alternative G-protein-independent ERK activation (JAK-2 and Src phosphorilation) revealed that they do not play a role in the SS-induced response. Finally, the efficacy of 3 different ARBs to block SS-induced activation of the AT1 in the absence of its ligand, Ang II, was tested. Interestingly, the original prototype compound, Losartan, showed the weaker ability to block AT1 activation by SS while Candesartan showed the higher ability and Telmisartan an intermediated response. Altogether, we provide evidence for the mechanical SS-induced activation of the AT1 and that ARBs display different efficacy to block this response suggesting that differences in chemical structure may play a role.

Key Words: mechanotransduction, angiotensin receptor, angiotensin receptor blockers.

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