Pharmacological reversal of endothelin-1 mediated constriction of the spiral modiolar artery: a potential new treatment for sudden sensorineural hearing loss.

Abstract:
BACKGROUND: Vasospasm of the spiral modiolar artery (SMA) may cause ischemic stroke of the inner ear. Endothelin-1 (ET-1) induces a strong, long-lasting constriction of the SMA by increasing contractile apparatus Ca2+ sensitivity via Rho-kinase. We therefore tested several Rho-kinase inhibitors and a cell-permeable analogue of cAMP (dbcAMP) for their ability to reverse ET-1-induced constriction and Ca2+-sensitization.

METHODS: The present study employed SMA isolated from gerbil temporal bones. Ca2+-sensitivity was evaluated by correlating vascular diameter and smooth muscle cell [Ca2+]i, measured by fluo-4-microfluorometry and videomicroscopy. RESULTS: The Rho-kinase inhibitors Y-27632, fasudil, and hydroxy-fasudil reversed ET-1-induced vasoconstriction with an IC50 of 3, 15, and 111 mumol/L, respectively. DbcAMP stimulated a dose-dependent vasodilation (Ec50 = 1 mmol/L) and a reduction of [Ca2+]i (EC50 = 0.3 mumol/L) of ET-1-preconstricted vessels (1 nmol/L). Fasudil and dbcAMP both reversed the ET-1-induced increase in Ca2+ sensitivity. CONCLUSION: Rho-kinase inhibition and dbcAMP reversed ET-1-induced vasoconstriction and Ca2+-sensitization. Therefore, Rho-kinase inhibitors or cAMP modulators could possess promise as pharmacological tools for the
treatment of ET-1-induced constriction, ischemic stroke and sudden hearing loss.

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