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POTENTIATION OF THE FIBROMYALGIA-ASSOCIATED PAIN BY ANGIOTENSIN I CONVERTING ENZYME INHIBITOR DRUGS[1]

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Introduction

Fibromyalgia is a disease potentially disabling, characterized by widespread chronic pain and a range of comorbidities as depression, fatigue, hypertension, among others. The hypertension, for example, affects 12–40% of patients with fibromyalgia. Studies showed that angiotensin I converting enzyme (ACE) inhibitors, commonly used antihypertensive drugs, can enhance the pain symptoms by blocking the neuropeptides degradation as substance P and bradykinin, besides enhancing kinin B_1 and B_2 receptors signaling.

Objective

Investigate the effect of ACE inhibitors on reserpine-induced fibromyalgia-associated pain and the kinin involvement on this effect.

Methods

The fibromyalgia model was induced by subcutaneous (s.c.) administration of reserpine (1 mg/kg, s.c.) once a day for three consecutive daysin adult male Swiss mice (CEUA:2770030516/2016 and 3189251018/2018-UFSM). The nociceptive parameter of mechanical allodynia was evaluated after the ACE inhibitors administration, captopril and enalapril (30 mg/kg, orally) in animals previously treated with reserpine. The role of kinin B_1 and B_2 receptors was investigated using pharmacological antagonism. Additionally, bradykinin levels, as well as the activity of ACE were measured in the sciatic nerve, spinal cord and cerebral cortex of the mice.

Results

ACE inhibitors enalapril and captopril enhanced the reserpine-induced mechanical allodynia from 1 up to 4 h after treatments with maximum effect of 44±8% and 45±10% at 1 h and 2 h after treatments, respectively. The treatment with kinin B_1 (DALBk) or B_2 (Icatibant) receptor

antagonists reduced the mechanical allodynia induced by reserpine plus enalapril administration from 0.5 up to 4 h after antagonists' administration. Maximal inhibitions (I_{max}) for DALBK and Icatibant were of 54±4% and 71±9% at 1 h after treatments, respectively. Likewise, DALBk and Icatibant reduced the mechanical allodynia induced by reserpine plus captopril administration from 1 up to 2 h and from 1 up to 4 h after antagonist's administration with I_{max} of 57±5% and 73±8% at 1 after treatments, respectively. The reserpine administrations or reserpine plus ACE inhibitor enalapril increased the bradykinin-related peptide levels in the sciatic nerve and cerebral cortex, but not in the spinal cord. However, treatment with reserpine plus ACE inhibitor captopril caused this increase in the sciatic nerve, cerebral cortex and spinal cord. Moreover, the enalapril and captopril administration enhanced the increase in the bradykinin-related peptide levels induced by reserpine in the cerebral cortex. The reserpine did not alter the ACE activity in the tissues evaluated. However, the treatment with reserpine plus ACE inhibitors enalapril and captopril was able to inhibit ACE activity in the sciatic nerve and cerebral cortex. Only the treatment with reserpine plus ACE inhibitor captopril was able to inhibit ACE activity in the spinal cord.

Conclusion

Since hypertension is a frequent comorbidity affecting fibromyalgia patients, the treatment of hypertension with ACE inhibitors by these patients should be reviewed since this could enhance the fibromyalgia-associated pain. Our results also point out the use of kinin receptor antagonists to treat the ACE inhibitors-induced enhanced pain.

Key words: mechanical allodynia, enalapril, spontaneous nociception, bradykinin.

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