VASORELAXANT AND ANTIOXIDANT EFFECTS OF THE NOVEL COMPOUND AP 2131

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Background. In the attempt to obtain new molecules endowed with L-type Ca2+ entry blocker properties, we have synthesized a group of compounds (APs) that have a common chemical structure, namely 9,10-endo-[α,β-succinimide]-anthracene, in which chloride has been added in different positions to obtain substances that differ each other only for the position of chloride on the anthracene group. This structure has been chosen for the following reasons: i) its good overlapping with that of nifedipine, a well known Ca2+ antagonist belonging to the dihydropiridines; ii) its rigid structure, which allows to simplify structure-activity relationship studies; iii) the observation that anthracen-9-carboxylic acid is a blocker of chloride channels.
Aim of the study. In this study we have investigated if one these compounds, named AP 2131, could show relaxant properties in vascular smooth muscle; also we have evaluated the effect of AP 2131 on the expression of heme oxygenase-1 (HO-1) and $p22^{phox}$, which are involved in the oxidative stress.
Methods. The relaxing effect of AP 2131 has been evaluated in rat caudal artery rings precontracted with 90 mM KCl or 10 μM phenylephrine. The rings, deprived of the endothelium, were mounted on custom-built plexiglass supports and were connected by tungsten wires to an isometric force transducer coupled to a pen recorder. The experiments were carried out at a temperature of 37 °C and pH 7,35. The activity of AP 2131 on the expression of (HO-1) and $p22^{phox}$ has been determined by RT-PCR in human lynphocytes
Results. AP 2131 (1-50 μM) concentration-depentently relaxed both KCl- and phenylephrine- contracted rat caudal artery rings with an EC_{50} of 6.1 (KCl) and 12 μM (phenylephrine. At the highest concentration, AP 2131 completely relaxed KCl-induced contraction, while the phenylephrine contraction was relaxed by 85%. Caffeine-evoked contractions, which are due to Ca2+ release by sarcoplasmic reticulum, were not affected by maximal AP 2131 concentrations, whereas, phenylephrine-induced contraction in Ca2+-free medium were slightly affected (-15%).
AP 2131, at concentrations that induced maximal relaxing effect on rat caudal artery rings (50 μM), reduced (HO-1) and $p22^{phox}$ gene expression in human lymphocytes. The reduction was -30% and –48% for HO-1 and $p22^{phox}$ respectively.
Conclusions. The pattern of action of AP 2131 in rat caudal artery is fully compatible with a Ca2+ entry blocker activity. In addition, our results suggest that AP 2131 may have protective effect against the oxidative stress.