RELAXING EFFECTS OF IMIDAZOBENZODIAZEPINE MP-III-058 ON RAT AORTA AND TRACHEA

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The role of $GABA_A$ receptors in the periphery has become increasingly important. Considering the molecular evidence of expression of the α5 subunit of the $GABA_A$ receptor in vascular and airway smooth muscle, the relaxant potencial of MP-III-058 (methyl (R)-8-bromo-6-(2-fluorophenyl)-4-methyl-4H-benzo[f]imidazo[1,5-a][1,4]diazepine-3-carboxylate), a selective ligand with hight efficiency on α5-containing $GABA_A$ receptors has been investigated.
The isometric tissue bath system was used to test the ability of MP-III-058 to relax the isolated rat aortic and tracheal rings. The rings were precontracted with phenylephrine ($3x10^{-6}$ M) or acetylcholine (3×10^{-5} M). Additionally, the effects of ligand MP-III-058 on phenylephrine-induced contraction were studied in two concentrations (10^{-5} M and 10^{-4} M).
The maximal relaxant effects of MP-III-058 (92.88±6.82% for aortic rings (n=7) and 53.21±7.02% for tracheal rings (n=12)) were achieved at the highest concentration of 10^{-4} M, and were significantly different ($p < 0.001$) from the respective vehicle controls (15.83±4.23% (n=6) and 6.31±3.39 % (n=4)). Also, there were statistically significant differences ($p < 0.001$) in phenylephrine-induced contractions in the presence of MP-III-058, compared to the control response. At both applied concentration, ligand MP-III-058 produced a significant rightward shift and decreased the maximal contraction in the phenylephrine concentration-response curves.
The present work emphasizes the role of peripheral $GABA_A$ receptors in vascular and airway smooth muscles relaxation. However, further *in vitro* studies are required to determine preclinical relevance for MP-III-058.

Keywords: Concentration-relaxation curve; Selective α5-containing $GABA_A$ ligand; tissue bath experiments