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Vascular effects of Tinuvin 770 in the isolated, perfused mesenteric artery of the rat.

Method

Male Sprague-Dawley rats (Tif;RAlf Sisseln) weighing 280-360 g were used. Animals were anaesthetised with ether and both carotid arteries were cut to allow exanguination. The superior mesenteric artery was cannulated via the abdominal aorta, and the mesenteric arterial bed (MAB) dissected free at its border with the intestine, according to a modification of the method of McGregor (1965). MABs were mounted and perfused at a constant rate of 5 ml/min. (Ismatec mp13GJ-4) with Tyrode's physiological perfusion solution (P.P.S.), the composition of which was (millimolar concentrations): NaCl (136); KCl (2.5); $MgCl_2$ (0.5), $CaCl_2$-(1.36); $NaHCO_3$ (11.9); NaH_2PO_4. (0.42). The solution was maintained at room temperature and continuously gassed with 95% O_2/5% CO_2 to give a pH of 7.2-7.4. Perfusion pressure (P.P.), which under constant flow conditions is proportional to vascular resistance, was measured using a Statham P23Db transducer via a side arm of the arterial cannula, and recorded continuously (Hellige). The MAB's were left for approximately 2 hours to stabilize before the experiments were begun. Noradrenaline (2ug, NA) and KCl (150 µmol) were added as a 0.5-ml bolus injection directly into the perfusion system by a peristaltic pump (Ismatec JPN 12) at intervals of 5 min alternately, in the presence or absence (controls, n=4) of cumulative concentrations of the test compound (O.0l, 0.1, 1. and 10 µM n=4). A 0.5 mM solution of the compound was prepared in 20% DMSO and further diluted in 10% DMSO. Controls were infused with an appropriate dilution of solvent. The infusion of of the solvent or the compound was done at a rate of 0.1 ml/min with a peristaltic pump (Ismatec MP 25 GJ-4). Each concentration was infused for 30 min. The value of the vasoconstrictor response for each agent obtained just before start of the compound or solvent was taken as the initial value and expressed as 100%.

Results

DMSO at the final concentration of 0.2 % slightly inhibited the increase in perfusion pressure induced either by NA or KCl (6% and 9% respectively). The DMSO concentration of 0.4% inhibited NA and KCl effects by 30% and 23 % respectively. Compared to these solvent effects, Tinuvin 770 was ineffective at concentrations between 0.01 and 1 µM , whereas at 10 µM it inhibited KCl-induced increase in perfusion pressure by 53%, without affecting NA-induced vasoconstriction.

Conclusions

These data indicate that Tinuvin 770 is inactive at final concentrations between 0.01 and 1 µM. At the highest concentration tested (10 µM) Tinuvin 770 exibited a preferential inhibition of KCl-induced vasoconstriction, indicating a possible effect at the calcium channel. Compared to other classical calcium antagonists, Tinuvin 770 was about 21- and 18-fold less active than verapamil and diltiazem respectively.

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(b) (4)