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Poster presentation

Effect of new sildenafil analogues in the rabbit isolated aorta

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Background

Nitric oxide (NO) diffuses into vascular smooth muscle cells to cause stimulation of guanylyl cyclase to elevate cGMP. The accumulated cGMP is degraded by phosphodiesterase-5 (PDE5) in cavernosal and vascular smooth muscle (Boollel et al., 1996). PDE5 inhibitors, such as sildenafil (SILD), block the degradation of cGMP, and lead vasorelaxation through increases in cGMP levels. The major side-effect of PDE5 inhibitors is associated with vasodilatation, producing a significant hypotension in individuals who take organic nitrates.

Purpose

The search for a more potent and selective PDE5 inhibitors has been our goal to develop sildenafil analogues, in order to alleviate the side-effects of sildenafil. Therefore, we aimed to compare the relaxing effects of 5-{2-Ethoxy-5-[(4-(4-fluorophenyl) piperazinylsulphonyl]phenyl)-1-methyl-3-N-propyl-1,6-dihydro-7*H*-pyrazolo [4,3-d]pyrimidin-7-one (SILD-6f), 5-(2-Ethoxy-5-(N-ethanol, N'-5-(2-ethoxy-5-sulphonyl)phenyl)-1-methyl-3-N-propyl-1,6-dihydro-7*H*-pyrazolo [4,3-d]pyrimidin-7-one-ethylenediamine-ulphonyl)phenyl)-1-methyl-3-N-propyl-1,6-dihydro-7*H*-pyrazolo [4,3-d]pyrimidin-7-one (SILD-6v) and 5-(2-Ethoxy-5-(N-phenyl-ethylenediamine-sulphonyl)phenyl)-1-methyl-3-N-propyl-1,6-dihydro-7*H*-pyrazolo [4,3-d]pyrimidin-7-one (SILD-6r) in rabbit isolated aorta (RbA).

Methods

Endothelium intact (E+) and denuded (E-) rings of RbA were mounted in organ baths. Data were recorded in a PowerLab system. Concentration-response curves (CRC) to SILD, SILD-6f, SILD-6v and SILD-6r (100 pM to 10 μM) were obtained in the absence or in the presence of soluble guanylyl cyclase (sGC) activator BAY 42–2272 (30 nM), nitric oxide synthase or sGC inhibitors, L-NAME (100 μM) or ODQ (10 μM), respectively. CRC for gliceryl trinitratate (GTN, 100 pM-10 μM) were constructed in the absence and in the presence of sildenafil analogues.

Results

In E+ rings, SILD-6f, 6v and 6r caused relaxations in a concentration-dependent manner, with potency (pEC_{50}) values of 7.28 ± 0.10, 6.93 ± 0.12 and 7.21 ± 0.10, respectively, which were similar to the pEC_{50} for SILD (7.25 ± 0.06) (Fig. 1a–d). Endothelium denudation caused a rightward shift in the CRC for SILD and SILD-6f (approximately 4-fold) without modifying the CRC to SILD-6v and SILD-6r. Addition of either L-NAME or ODQ reduced pEC_{50} in E+ rings similar to endothelium denudation for SILD and SILD-6f. No additional shift was seen in E- rings. Neither L-NAME nor ODQ affected relaxations evoked by SILD-6v or SILD-6r. Addition of BAY 42–2272 (30 nM) enhanced the pEC_{50} for SILD-6f, SILD-6v and SILD-6r in both E+ and E- rings (E+: 7.78 ± 0.08; 7.41 ± 0.09; 7.60 ± 0.07 and E-: 7.23 ± 0.07; 7.41 ± 0.09; 7.50 ± 0.08, respectively (Fig. 1). PDE5 inhibitors significantly

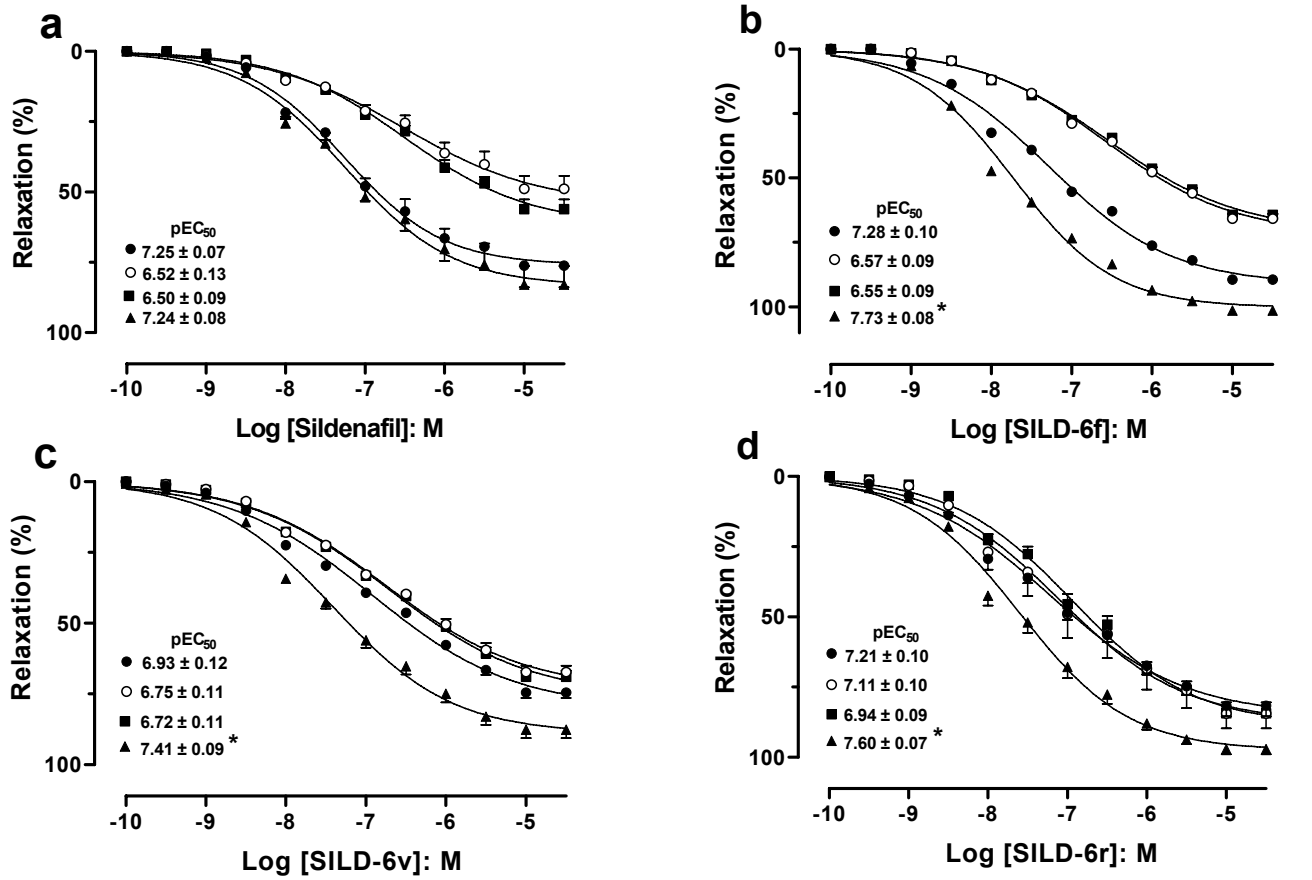

Figure 1
CRC to Sildenafil (panel **a**), SILD-6f (panel **b**), SILD-6v (panel **c**) and SILD-6r (panel **d**) in E+ aortic rings (100 pM – 10 μM) pre-contracted with PE (1 μM). Curves were constructed in the absence (filled circles) or in the presence of L-NAME (100 μM; open circles) or ODQ (10 μM; filled squares) or BAY 41–2272 (30 nM; filled triangles). Experimental values of relaxation were calculated relative to the precontraction level. Data are the mean ± SEM of 4–6 experiments. *P < 0.05 compared to each control value.

potentiated relaxations mediated by GTN (3, 3 and 4-fold, respectively for SILD-6f, SILD-6v and SILD-6r).

Conclusion

Sildenafil and SILD-6f relax the RbA by a mechanism partially endothelium-dependent. According our results, sGC stimulator significantly potentiates the relaxation evoked by SILD-6f, 6v and 6r. In contrast to SILD and SILD-6f, the basal release of NO endogenous does not apparently affected the vasorelaxant response to SILD-6v and SILD-6r.

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