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Relaxant effect of BAY 41–2272 in the rabbit isolated detrusor smooth muscle (DSM): involvement of cGMP-independent mechanisms

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Background

Overactive bladder (OAB) is described as urgency with or without incontinence, usually accompanied by frequency and nocturia. Overactive bladder reflects involuntary DSM as a consequence of enhanced cholinergic-mediated contractions and decreased b-adrenoceptor-mediated relaxations. The nitric oxide (NO)-cyclic GMP signaling pathway has been described to modulate the muscular tone, neurotransmission and blood flow in DSM, but the exact role of NO in the bladder is not completely understood. It is accepted that NO deficiency contributes to triggering OAB. The compound BAY 41–2272 has been described as a drug that directly activates the soluble guanylate cyclase leading to NO-independent cGMP accumulation. BAY 41–2272 produces potent relaxations in vascular and non-vascular smooth muscle tissues by cGMP-dependent and independent mechanisms, but no studies have been carried out with DSM.

Purpose

The aim of this study was to evaluate the relaxant effect of BAY 41–2272 in the rabbit isolated bladder and the mechanisms underlying the relaxant responses.

Methods

The present study was approved by the Ethics Committee for Experimental Research of the State University of Campinas (UNICAMP). Male New Zealand White rabbits (3 kg) were anaesthetized with urethane (1 g/kg, i.v.) After exsanguination, the abdomen was opened and the bladder was removed and placed in Krebs solution. The DSM strips (2 × 4 × 10 mm) were suspended between two metal hooks and mounted in 10 ml organ baths containing with Krebs' solution at 37°C, pH 7.4, and aerated continuously with 95% O_2 and 5% CO_2. The development of isometric tension was registered using force transducers connected to a PowerLab 400™ data-acquisition system (ADInstruments, MA, USA). Tissue preparations were equilibrated for 1 h before the start of the experiments. Initially, DSM preparations were challenged with 80 mM KCl to confirm tissue viability. Concentration-response curves for BAY 41–2272 (0.001–10 μM) were contructed in the presence and in the absence of L-NAME (100 μM), ODQ (10 μM) or sildenafil (0.1 μM) The relaxations were plotted as percentages of the contraction induced by carbachol (10 μM). Concentration-response curves to sodium nitroprusside (SNP, 0.01–10 μM) and gliceryl trinitate (GTN, 0.01–10 μM) were also constructed.

Results

BAY 41–2272 produced a concentration-response curve (Fig. 1a) in isolated DSM with a potency (pEC_{50}) and maximal response (E_{max}) of 6.71 ± 0.13 and 134.97 ± 4.84, respectively. The pEC_{50} values for BAY 41–2272 were higher than for SNP (6.04 ± 0.15), but not statistically different from GTN (6.37 ± 0.21). The E_{max} values for BAY were signicantly higher ($p < 0.001$) than those for SNP (48.87 ± 3.62) and GTN 41.94 ± 4.10.

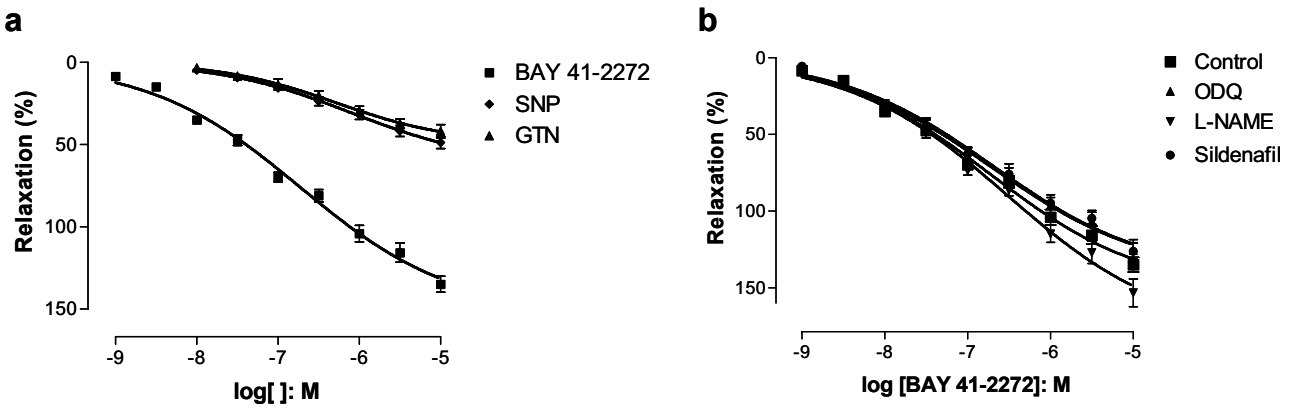

Figure 1
Relaxant effects of BAY 41–2272, sodium nitroprusside (SNP) and glyceryl trinitrate (GTN) (Panel A) and effect of L-NAME, ODQ and sildenafil in the BAY 41–2272 induced-responses (Panel B) in the rabbit isolated detrusor smooth muscle.

The potency of BAY 41–2272 was not significantly altered in the presence of L-NAME (6.37 ± 0.33), ODQ (6.66 ± 0.15) or sildenafil (6.67 ± 0.20) in comparison with vehicle (6.72 ± 0.12). Similarly the E_{max}values were not altered in the presence of L-NAME (153.30 ± 9.02), ODQ (125.69 ± 7.06) and sildenafil (126.18 ± 5.14) compared with vehicle (134.97 ± 4.84) (Fig. 1b).

Conclusion

In contrast with NO donors, BAY 41–2272 causes a complete relaxation of rabbit DSM. Our findings that relaxant responses to BAY 41–2272 are unaltered by L-NAME, ODQ and sildenafil indicate that BAY 41–2272 acts in an cGMP-independent manner to produce DSM relaxations. Therefore, BAY 41–2272 constitutes a drug with great potential to treat overactive bladder.