

MECHANISMS OF RELAXANT ACTIVITY OF THE NITRIC OXIDE-INDEPENDENT SOLUBLE GUANYLYL CYCLASE STIMULATOR BAY 41-2272 IN ISOLATED HUMAN URETER: AN IN VITRO STUDY

Hypothesis / aims of study

The compound 5-Cyclopropyl-2-[1-(2-fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-pyrimidin-4-ylamine (BAY 41-2272) is a potent nitric oxide (NO)-independent soluble guanylyl cyclase stimulator [1,2], but little is known about its effects in the upper urinary tract. This study aimed to investigate the mechanisms underlying the relaxation activity of isolated human ureter specimen induced by BAY 41-2272.

Study design, materials and methods

The 3-cm distal portion of human ureter strips were harvested from renal cadaveric donors. Ureteral ring was cut open and tissue was vertically mounted in 10-ml organ baths for isometric force recording.

Ureteral tissue was pre-contracted with potassium chloride (KCl) before relaxing activity of BAY 41-2272 was assessed. Prior incubation with the NO synthesis inhibitor L-NAME (100 microM), soluble guanylyl cyclase inhibitor ODQ (10 microM), type 5 phosphodiesterase inhibitor Sildenafil (100nM) and sodium nitroprusside was performed to evaluate BAY 41-2272 potentiating or inhibitory action.

Results

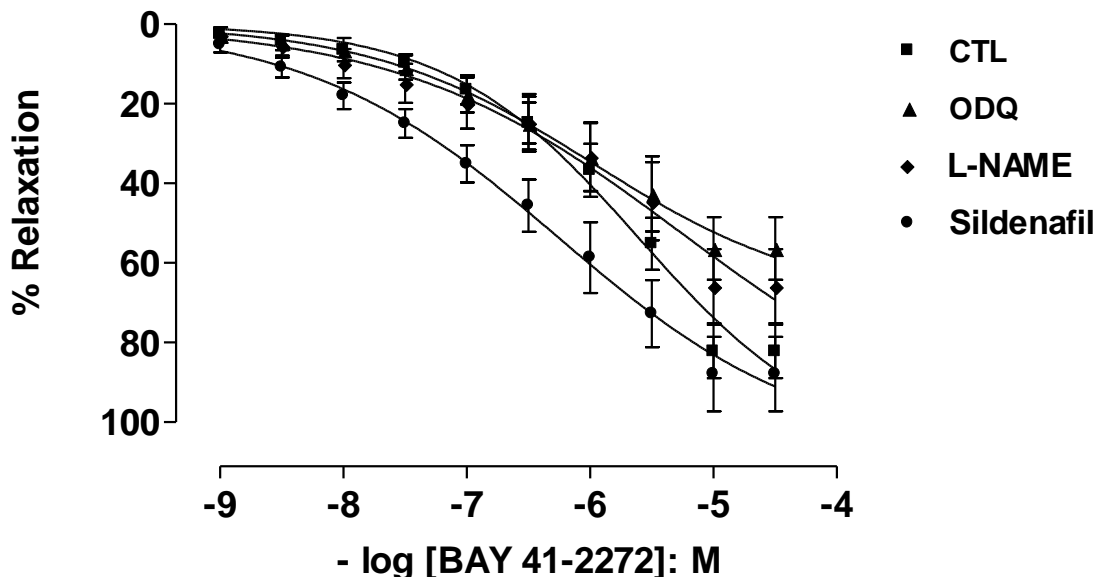
BAY 41-2272 concentration-dependently relaxed strips pre-contracted with KCl with potency (pEC_{50}) and maximal response (E_{max}) values of 5.62 ± 0.29 and $88 \pm 8\%$, $n=7$ ($P<0.05$), respectively. Prior incubation with L-NAME or ODQ caused significant decrease (65 ± 9 and $56 \pm 7\%$, $n=5$, $P<0.05$, respectively) on the E_{max} values. Prior addition of sildenafil produced a leftward shift (6.25 ± 0.16 , $n=4$) on the relaxation induced by BAY 41-2272. Sodium nitroprusside also caused concentration-dependent relaxations (pEC_{50} : 5.92 ± 0.03 , $n=3$) in human ureter, which were greatly potentiated by BAY 41-2272 ($1 \mu M$, PEC_{50} : 6.36 ± 0.04 , $n=4$, $P<0.05$).

Interpretation of results

As direct inhibitors of the NO synthase enzyme and of the guanylyl cyclase, respectively, L-NAME and ODQ have both the same ultimate effect which is to decrease the amount of GMPc available. This turned out to decrease ureteral elasticity proving this route to be of major importance in ureteral relaxation. Accordingly, sildenafil as a type 5 phosphodiesterase inhibitor was able to increase ureteral relaxation, as it reduces GMPc degradation. At last, sodium nitroprusside also had a synergistic action in relaxing the ureter, as NO donor.

Concluding message

Our findings show that BAY 41-2242 relaxed human ureter and this relaxation was partially dependent on the accumulation of the cyclic guanosine monophosphate (cGMP). Thus, BAY 41-2272 might have a clinical role in relieving ureteral colic pain, facilitating spontaneous stone passage or acting as an adjunctive therapy to extracorporeal shock-wave lithotripsy [3].



References

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None

Is this a clinical trial?

No

What were the subjects in the study?

NONE
