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BAY 58-2667, A SOLUBLE GUANYLYL CYCLASE ACTIVATOR, PREVENTS CYCLOPHOSPHAMIDE INDUCED CYSTITIS IN MICE.

Hypothesis / aims of study

Interstitial cystitis (IC) is a chronic inflammatory disorder characterized by suprapubic pain, discomfort, excessive urgency and urinary frequency, besides profound effects on patient's quality of life. Cyclophosphamide (CYP) is commonly used as an experimental model for the investigation of IC because of its similarity with the human disease (1). Studies demonstrate that extensive oxidative stress during inflammation compromise bladder function by impairing the nitric oxide (NO)-soluble guanylyl cyclase (sGC)-cGMP signaling. NO independent sGC activators have high affinity for NO-insensitive/oxidized form of sGC and increase cGMP production by restoring the sGC signalling (2). This study aimed to evaluate whether sGC activation by BAY 58-2667 prevents CYP-induced cystitis.

Study design, materials and methods

Eight to ten-weeks-old C57BL/6 female mice (20-25 g) were pre-treated with BAY 58-2667 0.5 mg/kg or its vehicle (Transcutol®: Cremophor®: water, 1:2:7, v/v/v %) by gavage (0.2 mL/animal). After 1 h the animals were treated with CYP (300 mg/kg, i.p) or saline (5 mL/kg, i.p). Studies were performed at 24 h after CYP administration. The gross evaluation of the bladder was performed to assess the IC severity including body/bladder wet weight ratio and hemorrhage. For micturition pattern analysis, mice were placed in cages individually and urine output was collected for 1 h on filter paper covering the cage bottom, photographed under UV light and analyzed to identify the surface area of individual spots. Volume of micturition was calculated based on a calibration curve relating surface area to urine drops of know volume (3). Cystometry was performed in urethane-anesthetized mice. Bladders were filled at a constant rate (0.6 mL/h) and intravesical pressure was recorded for 30 min.

Results

CYP-injected mice exhibited increased body/bladder weight ratio and hemorrhagic score compared to control (P<0.001), which was prevented by BAY 58-2667 treatment (P<0.01). Micturition pattern analysis of control and CYP groups shows a remarkable increase in the number of spots (4.6 ± 1.5 and 161 ± 2.6) and micturition volume (0.47 ± 0.082 and 0.024 ± 0.005), which was significantly prevented by BAY 58-2667 (P<0.05 and P<0.001, respectively). Cystometric studies show significant changes in several micturition patterns in CYP group compared to control, including basal pressure, bladder capacity, voiding frequency and NVCs. BAY 58-2667 treatment significantly prevented these alterations (Table 1).

Table 1. Comparative cystometric parameters among different experimental groups.

	Control	BAY	CYP	BAY + CYP
Basal pressure (mmHg)	2.50 ± 0.35	1.18 ± 0.21	6.32 ± 0.34***	2.94 ± 0.71$^{\#\#\#}$
Bladder capacity (ml/h)	0.12 ± 0.05	0.12 ± 0.01	0.01 ± 0.01*	0.06 ± 0.02$^{\#}$
Threshold pressure (mmHg)	5.67 ± 1.90	6.98 ± 0.61	5.27 ± 1.95	5.35 ± 0.85
Peak pressure (mmHg)	22.8 ± 2.55	28.3 ± 1.56	22.1 ± 5.37	24.2 ± 3.81
Voiding frequency (number/min)	0.12 ± 0.02	0.16 ± 0.02	0.86 ± 0.25*	0.46 ± 0.17$^{\#}$
NVCs frequency (number/min)	0.50 ± 0.15	0.42 ± 0.07	2.93 ± 1.00*	0.82 ± 0.31$^{\#}$

Data represents the mean ± SEM for 5-6 animals each group. One-way ANOVA followed by Tukey's test; $^{*}P$<0.05, $^{***}P$<0.001 compared with control group; $^{\#}P$<0.05, $^{\#\#\#}P$<0.001 compared with CYP group.

Interpretation of results

CYP caused pronounced urinary bladder inflammation and bladder overactivity. BAY 58-2667 pre-treatment prevented significantly these alterations, ameliorating the bladder dysfunction.

Concluding message

Activation of sGC-cGMP signaling pathway by sGC activators confers a protective effect in CYP-induced cystitis, providing a potential therapeutic target for IC.

References

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Disclosures

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