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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INHIBITS FREQUENCY AND VOLUME OF MICTURITION TEMPORARY IN MALE RAT: DIFFERENCE BETWEEN CONSCIOUS AND ANESTHETIZED RATS

Hypothesis / aims of study

Prostaglandin (PG) E2 receptors are in various site of the micturition reflex pathway. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes, which transform PGs from arachidonic acid. NSAIDs have been used widely for various inflammations. Under urethane anesthesia, NSAIDs inhibited intercontruction interval (ICI) in acute inflammation of the urinary bladder with cyclophosphamide treatment (1). Recent study demonstrated that NSAIDs reduced nocturia (2). Thus PGE2 might be involved in normal micturiton reflex in addition to acute inflammation of urinary bladder. Since PGE2 release was changed with anesthesia, it is important to study the NSAIDs effects on micturition reflex under conscious condition for studying the physiological role. This study is to examine the effect of non-selective COX inhibiter, loxoprofen, on number and volume of micturiton reflex in conscious rats using metabolic cage. In addition, we examined the cystometrograms (CMG) in conscious and/or in urethane anesthesia rats. Farther, we measured PGE2 in the collected urine or in the CMG infusion solution for determine the site of action.

Study design, materials and methods

We used Sprague-Dawely male rat, weighting 300 to 450 gm. 1) Metabolic cage study: we let rats into metabolic cage in a room with a 12/12-hour light dark cycle. The dark cycle started at 7:00 PM. Number of micturition and urine volume was measured. 0.5ml loxoprofen or 0.5 ml distilled water (for control) was given orally at 6:00 PM. Since micturition of the rat was varying in 24 hours, the control date was measured at same time of the day of prior to loxoprofen administration. 2) Continuous CMG: CMG (constant infusion of saline rate 2.4 ml/min) was performed in restrained cage on conscious or anesthetized rats. 3) Correction of urine from bladder: After cystostomy and canulation of the bladder, urine was corrected in the restrained cage. Saline transfusion (4 ml/kg/hr) maintained for reasonabe amount of urine production. 4) PGE2 measurements: PGE2 measured in the collected urine using RIA DCC method.

Results

1) Metabolic cage: We administrated loxoprofen (1 mg/kg, PO, n=43) at 6:00 PM. Averaged number and volume of micturition in next 4 hours (6:00-10:00 PM) was reduce. The number reduced from 3.4±0.2 to 2.6±0.2 (75%, $P<0.01$). The volume changed 2.1±0.1 g to 1.4±0.1 g (63.1%, $P<0.01$, fig.1). In contrast, averaged number or volume of micturition in 23 hours did not change significantly after administration of loxoprofen. (20.4±0.9 to20.6±0.8, 12.9±0.5 g to 12.8±0.5 g, respectively). Low dose of loxoprofen (0.01–0.1 mg, n=8 each) was not altered the number and volume of micturition. Reduction of the number and volume was proportional to the dose-response at range from 0.3 mg/kg to 3 mg (n=8). The number of micturition reduced to 92 %, 79 %, and 63 % (0.3mg, 1mg, and 3mg, respectively). The volume reduced to 74 %, 53 %, and 44 % (0.3mg, 1mg, and 3mg, respectively).
2) Continuous CMG: In conscious rats (n=9), loxoprofen (1 mg/kg, 0.2 ml i.v.) did not altered the any parameter of the continuous CMG (ICI; 15.5±2.7 to 17.2±2.8 minutes ($P=0.49$), the pressure threshold; 12.4±1.5 to 12.8±1.2 mmH2O, the maximal pressure; 39.0±2.7 mmH2O to 37.7±3.2 mmH2O). In anesthetized rats, loxoprofen (1mg/kg 0.2ml i.v.) prolonged ICI 25.1±3.6 to 49.6±9.7 minutes ($p<0.05$). However the pressure threshold and maximal pressure were not change (11.8±1.5 to 12.6±1.7 mmH2O, 44.3±2.8 mmH2O to 46.7±3.4 mmH2O, respectively).
3) Urine correction: Administration of loxoprofen (1 mg/kg, 0.1 ml i.v.) reduced urine volume from the bladder catheter. The control urine volume was 0.7±0.1 g/hr. The urine volume after the drug administration in next 4 hours was 0.4±0.1 g/hr ($P<0.05$), 0.4±0.1 g/hr, 0.6±0.2 g/hr, and 1.1±0.3g/hr, respectively.

4) PGE2 measurement: In the metabolic cage study, PGE2 in 4 hours reduced to 49% of control. In continuous CMG study, PGE2 reduced to 47% in conscious rats, PGE2 reduced to 7% in anesthetized rats. In urine correction study, PGE2 reduced to 61% of control.

		Conscious	Anesthetized
Metabolic cage	Number	75%	
	Volume	63%	
	PGE2	49%	No
CMG	ICI	111%	198%
	PGE2	47%	7%
Urine from cystostomy	Volume	60%	
	PGE2	61%	No

Table1. Summary of effects of loxoprofen in conscious or anesthetized rats.
Note: each date representing of % of control.

Interpretation of results

In conscious free moving rats, loxoprofen reduced number of micturition and voiding volume in first 4 hours. Loxoprofen reduced urine volume from the bladder catheter in conscious restrained rats. Loxoprofen did not change ICI in conscious rats. Thus reduction of urine volume is most likely the mechanism of loxoprofen for the temporary inhibition. In anesthetized rats, loxoprofen showed two different results from conscious rats. ICI was prolonged in the anesthetized rats. Reduction of PGE2 was predominantly larger in the anesthetized rats. These results suggested that in anesthetized condition, PGE2 might play important roles in micturition reflex in urinary bladder.

Concluding message

NSAIDs reduced the urine production might be cause temporary inhibition of micturition reflex in conscious rats. NSAIDs inhibited the micturition reflex stronger in anesthetized rats.

References

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