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INHIBITORY EFFECTS OF GABAPENTIN AND PREGABALIN ON THE MICTURITION REFLEX IN RATS

Hypothesis / aims of study

Gabapentin and pregabalin are compounds structurally related to γ-aminobutyric acid (GABA) with recognized efficacy in the treatment of epilepsy and neuropathic pain. Modest actions on the GABAergic neurotransmitter system as well as on voltage-gated Ca^{2+} channels containing the α2δ-1 subunit have been proposed.[1] Recently, it has also been reported that overactive bladder (OAB) was successfully treated with GBP[2,3] although the mechanism of action still remains unclear. The aim of this study was therefore to clarify the effects of gabapentin and pregabalin on bladder function by means of cystometrogram in normal rats.

Study design, materials and methods

In female SD rats under urethane anesthesia (1.2 g/kg, s.c.), a PE90 catheter was placed into the bladder from the bladder dome for bladder filling and pressure recording, and repetitive bladder contractions were elicited by saline infusion into the bladder (0.04 ml/min).

(1) Using a series of single cystometry, bladder capacity, threshold pressure for reflex bladder contractions (TP), micturition pressure (MP) and residual urine volume (RV) were measured before and 1 hour after the administration of gabapentin (10-30 mg/kg, i.p.) or pregabalin (10-30 mg/kg, i.p.).

(2) The effects of gabapentin (30 mg/kg, i.p.) were also studied in rats pre-treated with resiniferatoxin (RTX) (0.3 mg/kg, s.c., 3 days before the experiment), which induces desensitization of C-fiber afferents.

(3) Using continuous cystometry, ICI, BP, TP and MP were measured before and after the intravesical administration of gabapentin (10^{-2}M).

Results

(1) Both gabapentin and pregabalin significantly increased bladder capacity to 165 ± 14% (gabapentin 30 mg/kg) and 183 ± 11% (pregabalin 30 mg/kg) of the pre-drug control values while the vehicle treatment had no effects (Figure 1). They also significantly increased TP and RV. However, neither gabapentin nor pregabalin had significant effects on MP (Table 1).

(2) In rats with RTX pretreatment to desensitize C-fiber afferent pathways, gabapentin (30 mg/kg) increased bladder capacity at a similar degree to RTX-untreated rats (Table 1).

(3) In continuous cystometry, intravesical administration of gabapentin (10^{-2}M) had no significant effects on any of cystometric parameters (ICI, BP, TP or MP).

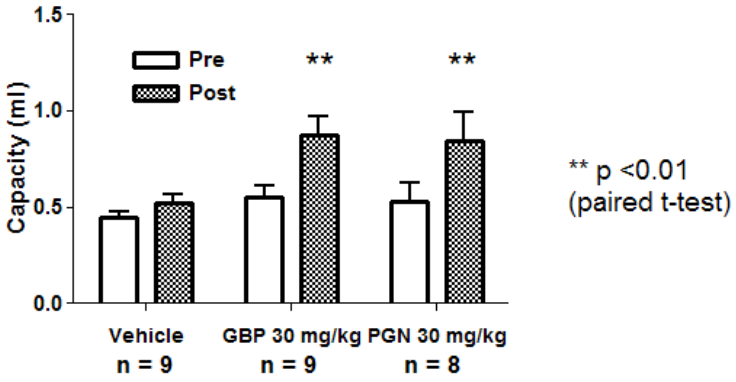

Figure 1. Effects of gabapentin (GBP) and pregabalin (PGN) on bladder capacity.

Interpretation of results

Both gabapentin and pregabalin significantly increased bladder capacity and pressure thresholds while having no effects on MP. These results suggest that these two drugs suppress the micturition reflex via inhibition of afferent signal transmission rather than bladder efferent function that controls bladder contractility. In addition, increased residual urine volume without significant changes in MP after gabapentin or pregabalin suggests that these two drugs might also have effects on urethral function to increase urethral resistance. Moreover, because the effects of gabapentin on bladder capacity were not blocked by RTX pretreatment, gabapentin may induce the effects at least in part by inhibition of bladder afferent pathways other than RTX-sensitive C-fiber afferents. The results also revealed that the site of action of gabapentin is not at the bladder level because the intravesical application of gabapentin did not affect any cystometric parameters.

Table 1. Effects of gabapentin (GBP) and pregabalin (PGN) on parameters in cystometry

		Cap (ml)	TP (cmH_2O)	RV (ml)	MP (cmH_2O)
GBP (30 mg/kg)	Pre	0.55 ± 0.06	6.2 ± 0.7	0.06 ± 0.02	34.2 ± 1.9
	Post	0.88 ± 0.09**	11.3 ± 1.8**	0.40 ± 0.09**	30.9 ± 1.5
PGN (30 mg/kg)	Pre	0.53 ± 0.10	5.7 ± 0.6	0.08 ± 0.03	33.8 ± 1.6
	Post	0.97 ± 0.18**	16.6 ± 3.1**	0.61 ± 0.15**	36.8 ± 1.9
GBP (30 mg/kg)	Pre	0.69 ± 0.09	8.4 ± 1.1	0.26 ± 0.09†	33.4 ± 1.8

(RTX pretreated)	Post	0.89 ± 0.11*	15.4 ± 4.4	0.54 ± 0.17*	35.2 ± 4.3

Cap: bladder capacity

** $p < 0.01$, * $p < 0.05$ before vs. after drug administration (paired t-test).

† $p < 0.05$ non-treated vs. RTX pretreated before drug administration (Student's t-test).

Concluding message

The results in this study indicate that gabapentin and pregabalin have inhibitory effects on the micturition reflex presumably via inhibition of bladder sensory pathways. This mechanism could explain the clinical efficacy of these drugs for the treatment of patients with OAB.

References

1. Curr Opin Pharmacol (2006) 6; 108-113.
2. Int Braz J Urol (2004) 30; 275-278.
3. Clin Neuropharmcol (2006) 29; 206-214.

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**University of Pittsburgh Institutional Animal Care and Use Committee**