



#154 TRPV4 receptor activation in the bladder improves voiding dysfunction in a rat model of detrusor underactivity induced by pelvic nerve crush injury

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Background:

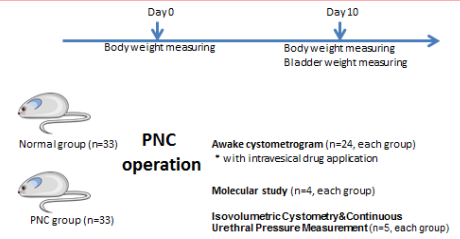
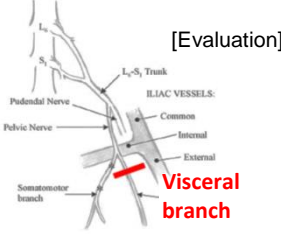
Incomplete bladder emptying due to detrusor underactivity (DU) is a significant problem underlying underactive bladder (UAB). Also, TRPV4 has been reported to be one of the mechanosensitive channels expressed in the bladder.

In this study, we sought to produce a consistent rat model of UAB with pelvic nerve crush (PNC) and evaluated the therapeutic effect of intravesical application of a TRPV4 agonist (GSK 1016790A) on the UAB condition.

Materials and Methods:

[Animal model]

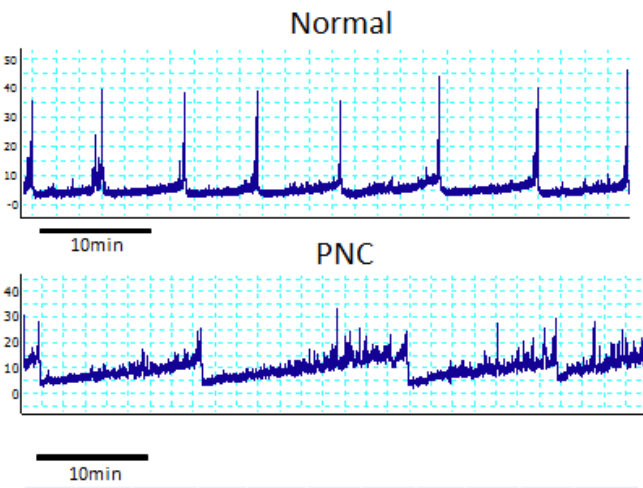
In Female Sprague-Dawley rats, the visceral branches of bilateral pelvic nerves were identified near the internal iliac vessels, and bilateral PNC was made by two times of nerve compression of either side with each 20-seconds duration using sharp forceps.



Results:

- Morphology: **Bladder weight** was significantly **increased** in PNC rats (Normal=0.078±0.012, PNC=0.22±0.012, p<0.0001).
- Awake CMG (Fig.1): PNC rats showed significant **increases in voided volume, post-void residual urine volume, and residual urine rate** compared to control rats. PNC rats also revealed the significant **increases in inter contraction intervals (ICI), a number of non-voiding contractions, and threshold pressure** while the **amplitude of bladder contraction** during voiding was significantly **decreased**.
- Intravesical TRPV4 administration to normal rats (Fig.2): Intravesical **1.5µM** of GSK 1016790A application did not significantly affect any CMG parameters.
- Intravesical TRPV4 administration to PNC rats (Fig.3): Intravesical **1.5µM** of GSK 1016790A significantly decreased ICI, voided volume, and post-void residual urine volume in PNC rats.
- mRNA expression of TRPV4 in the bladder mucosa was significantly increased in PNC rats compared to the normal rats (p=0.0013)(Fig.4).
- PNC rats exhibited **impaired urethral relaxation** during isovolumetric (ISO) bladder contraction (Fig.5).

Figure 1. Awake CMG of Normal and PNC rats



	ICI (s)	Amplitude (cmH2O)	PB (cmH2O)	PT (cmH2O)	NVC rate (NVC/min)	VV (µl)	RU (µl)	RU rate (%)	Capacity (µl)	Compliance (ml/cmH2O)
Normal (n=24)	370 ± 17	37 ± 2.6	3.9 ± 0.27	9.3 ± 0.5	0.063 ± 0.019	522 ± 28	4.5 ± 2.4	0.89 ± 0.51	530 ± 28	0.12 ± 0.013
PNC (n=24)	910 ± 61	28 ± 1.3	4.3 ± 0.4	15 ± 1.0	0.96 ± 0.15	995 ± 57	810 ± 170	40 ± 5.6	1799 ± 192	0.13 ± 0.010
P*	<0.0001	0.0057	0.35	<0.0001	<0.0001	<0.0001	0.0005	<0.0001	<0.0001	0.52

Figure 3. Intravesical GSK1016790A (1.5µM) administration to PNC rats

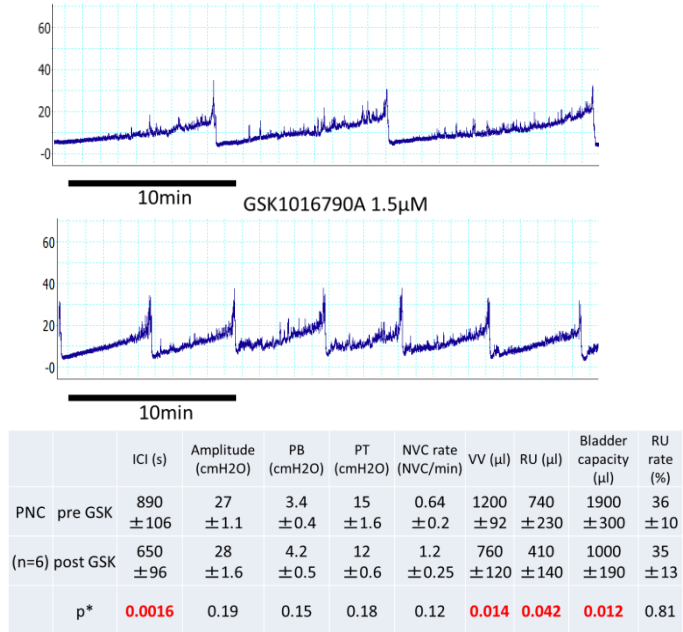


Figure 5. Isovolumetric Cystometry & Continuous Urethral Pressure Measurement

Figure 4. TRPV4 transcript levels in the bladder mucosa from normal and PNC rats

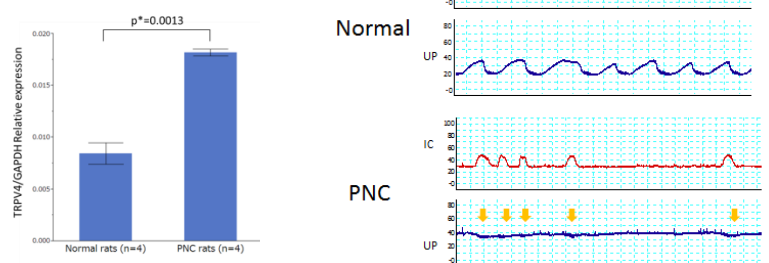
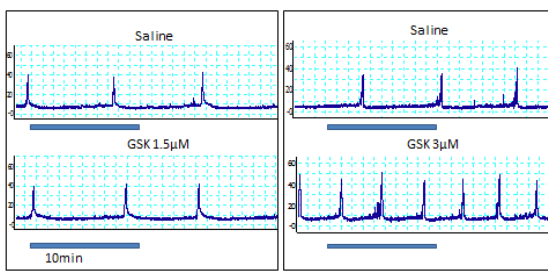
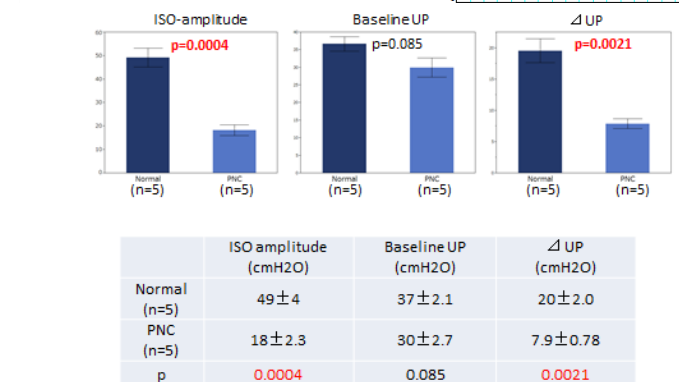


Figure 2. Intravesical GSK1016790A administration to Normal rats



	ICI (s)	Amplitude (cmH2O)	PB (cmH2O)	PT (cmH2O)	NVC rate (NVC/min)	VV (µl)	RU (µl)	RU rate (%)
0.1% DMSO (n=6)	393 ± 34	33 ± 3.6	3.5 ± 0.94	8.6 ± 0.93	0.15 ± 0.050	566 ± 44	9.2 ± 5.8	1.2 ± 0.8
saline	366 ± 16	33 ± 3.7	3.2 ± 0.60	8.5 ± 0.96	0.10 ± 0.066	572 ± 50	10 ± 6.3	1.4 ± 1.0
p*	0.33	0.81	0.61	0.9	0.49	0.84	0.17	0.38
GSK 0.3µM (n=6)	423 ± 40	35 ± 2.8	5.2 ± 0.39	10 ± 0.82	0.27 ± 0.16	552 ± 68	0.42 ± 0.42	0.063 ± 0.063
saline	424 ± 15	32 ± 1.8	4.4 ± 0.30	8.5 ± 0.23	0.054 ± 0.021	599 ± 40	5.0 ± 5.0	0.60 ± 0.60
p*	0.38	0.1	0.3	0.55	0.23	0.87	0.36	0.36
GSK 1.5µM (n=6)	356 ± 40	33 ± 3.7	7.1 ± 1.8	12 ± 3.1	0.12 ± 0.054	488 ± 50	4.6 ± 4.6	0.91 ± 0.91
saline	398 ± 35	32 ± 2.3	4.1 ± 0.42	8.5 ± 0.68	0.029 ± 0.015	550 ± 50	5.0 ± 5.0	0.87 ± 0.87
p*	0.085	0.5	0.13	0.23	0.16	0.087	0.36	0.36
GSK 3µM (n=6)	261 ± 43	35 ± 4.0	6.2 ± 1.5	11 ± 1.9	0.300 ± 0.089	343 ± 57	6.2 ± 6.2	2.2 ± 2.2
saline	393 ± 39	32 ± 2.8	3.7 ± 0.67	7.9 ± 0.54	0.038 ± 0.021	536 ± 60	12 ± 7.6	1.7 ± 2.9
p*	0.018	0.19	0.076	0.13	0.044	0.011	0.31	0.66



Conclusions:

- Rats with pelvic nerve injury induced by a PNC method, which showed the characteristics of DU, seem to be an appropriate model for evaluation of peripheral neurogenic mechanisms of UAB.
- TRPV4 that reduced the bladder capacity and residual urine volume in PNC rats could be a potential target for the treatment of UAB.
- PNC rats had impaired urethral relaxation. The therapy to enhance urethral relaxation may be effective for UAB treatment.