

URETHRAL COMPENSATORY MECHANISMS UNDERLYING THE RECOVERY OF URINARY CONTINENCE AFTER PUDENDAL NERVE INJURY IN FEMALE RATS

Hypothesis / aims of study

Stress urinary incontinence during pregnancy or after childbirth is common, but usually short-lasting and spontaneously disappears in most women. Thus, to clarify the urethral compensatory mechanism of urinary continence after childbirth, we performed a leak point pressure (LPP) testing and a urethral muscle strip study in female rats with pudendal nerve transection (PNT). In addition, sex difference was also investigated.

Study design, materials and methods

Sprague-Dawley male and female rats were used, and some female rats underwent PNT 4 weeks before the experiments (PNT-4w). Under isoflurane anesthesia, the spinal cord was transected at T8-9 level to suppress reflex bladder contractions and the bladder was filled with 0.3 ml saline. In PNT rats, pudendal nerves were transected bilaterally near the internal iliac vessels through a lower midline abdominal incision. Then, under urethane anesthesia, LPPs during manual lower abdominal compression were measured before and after the intravenous application of hexamethonium (C6; 25 mg/kg), which suppresses autonomic efferent nerve activity. When LPPs were increased after C6, the effects of cumulative application of propranolol (1 mg/kg) and/or N-nitro-L-arginine methyl ester (L-NAME; 20 mg/kg) were examined. When LPPs were decreased after C6, the effects of cumulative application of terazosin (0.3 mg/kg) and/or atropine (0.5 mg/kg) were investigated. In addition, proximal and middle urethral responses to carbachol or phenylephrine were examined in urethral muscle strips obtained from naive and PNT-4w female rats.

Results

In male rats, LPPs immediately after PNT (PNT-immediate) were significantly decreased by C6, as well as by terazosin and atropine applications (Fig.1A), indicating the contractile control of the urethra by adrenergic and cholinergic pathways. In female rats, LPPs immediately after PNT were significantly increased by C6, and these effects were similar to those seen after an application of L-NAME, but not propranolol (Fig.1B), indicating the relaxing control of the urethra by nitergic pathways. On the other hand, LPPs of PNT-4w female rats were significantly decreased by C6, and these effects were similar to those induced by terazosin and atropine (Fig.1C), indicating the shift from the nitergic control to the adrenergic and cholinergic controls during 4 weeks after PNT. In addition, there was no significant difference in LPPs of naive and PNT-4w female rats (Fig.2A) while LPPs of PNT-4w female rats after C6 application were significantly decreased compared with PNT-immediate or naive female rats (Fig.2B). In the muscle strip study, proximal, but not middle, urethral responses to carbachol or phenylephrine in PNT-4w female rats were significantly increased compared with naive female rats (Table 1).

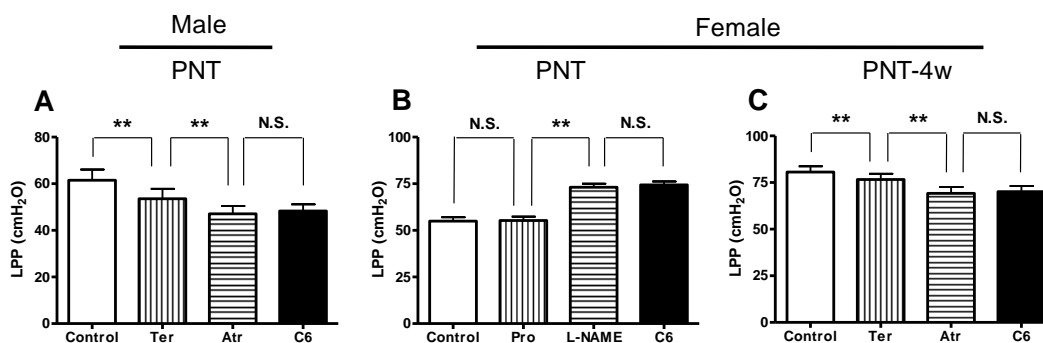


Fig.1. Changes in LPPs due to cumulative application of terazosin (Ter), atropine (Atr) and hexamethonium (C6) in PNT-immediate male rats (A) and PNT-4w female rats (C), or cumulative application of propranolol (Pro), N-nitro-L-arginine-methyl ester (L-NAME) and C6 in PNT-immediate female rats (B).

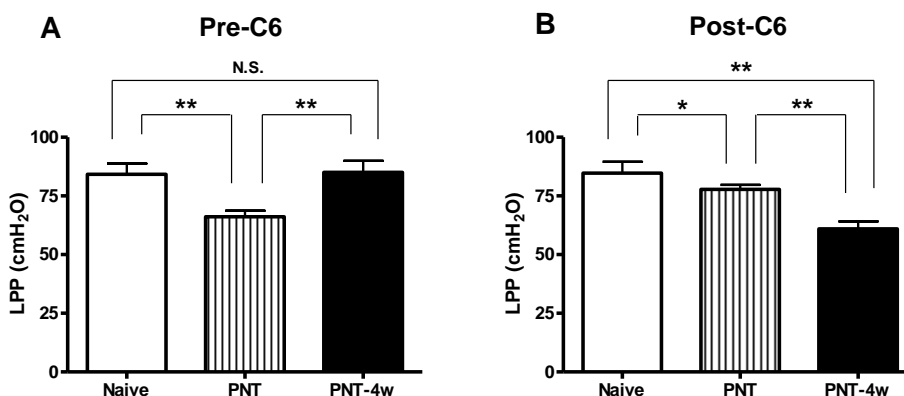


Fig.2. Comparison of LPPs in female rats with naive, PNT-immediate or PNT-4w before (A) and after (B) hexamethonium (C6) application.

Table 1. Contractile responses of proximal and middle urethral muscle strips to carbachol and phenylephrine in naive and PNT-4w female rats.

		EC ₅₀ (μM)	
		Proximal urethra	Middle urethra
Carbachol	Naive	3.8 ± 1.3	2.6 ± 1.2
	PNT-4w	1.5 ± 1.2**	1.8 ± 1.2
Phenylephrine	Naive	7.6 ± 1.3	2.8 ± 1.3
	PNT-4w	2.8 ± 1.3*	2.6 ± 1.2

Interpretation of results

These results suggest that in female rats 4 weeks after PNT the nitric oxide-induced relaxing effects are switched to contractile responses mediated by α_1 -adrenoceptors (ARs) and muscarinic receptors (MRs) at the proximal urethra, which are similarly seen in the responses of male rats.

Concluding message

We hypothesize that the proximal urethra in female rats is mainly controlled by relaxing nitrergic mechanisms under the normal condition during abdominal pressure increases; however it undergoes the compensatory process to counteract the deficient middle urethral function by enhancing α_1 -AR and MR activity after pudendal nerve injury, and that this mechanism may contribute to the functional recovery of urinary continence reflexes after childbirth.

<i>Specify source of funding or grant</i>	National Institutes of Health: DK067226, AR049398 and DK055387
<i>Is this a clinical trial?</i>	No
<i>What were the subjects in the study?</i>	ANIMAL
<i>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</i>	Yes
<i>Name of ethics committee</i>	University of Pittsburgh Institutional Animal Care and Use Committee