PRIZE AWARD: Best Basic Science Abstract (Joint)

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EFFECTS OF L-ARGININE ON SINGLE UNIT AFFERENT ACTIVITIES SYNCHRONIZED WITH RHYTHMIC BLADDER CONTRACTIONS IN THE RAT

Hypothesis / aims of study

It has been reported that nitric oxide (NO) can inhibit the mechanosensitive both Aδ- and C-fiber afferent activities during bladder distension in the rat (1). These afferent activities, however, may be enhanced also by bladder contractions (2). To determine the possibility, we have established the measurement of single unit mechanosensitive bladder afferent activities (SAAs) synchronized with rhythmic bladder contractions (RBCs), and investigated whether endogenous NO can affect the SAAs in such condition.

Study design, materials and methods

Female Sprague-Dawley rats were used. Under intraperitoneal urethane anesthesia (1.2 g/kg), for monitoring SAAs, fine filaments were dissected from the left L6 dorsal roots and placed across a bipolar electrode. Nerve fibers primarily originating from the bladder were identified by electrical stimulation of the left pelvic nerve and by bladder distension. Nerves of which conduction velocity (CV) is more than 2.5 m/sec were determined as Aδ-fibers and those with less than 2.5 m/sec as C-fibers (3). To produce the RBCs, right L6 dorsal roots were kept intact and the urethral meatus was clamped. After the bladder had been emptied, saline was instilled into the bladder at a rate of 0.16 ml/min. Bladder pressure and SAAs were recorded continuously on Spike2 program. When RBCs appeared, the instillation was stopped and the bladder was kept under an isovolumetric condition. After RBCs appeared reproducibly for a period of 5 minutes, vehicle (saline) or L-arginine (an NO substrate, 300 mg/kg) was administrated intravenously, and parameters of bladder pressure and SAAs were analysed during 3 or 4 of RBCs before and after the drug-administartion (Figure 1).

Results

Among the bladder pressure parameters analyzed, the amplitude and duration of RBCs did not change after vehicle- or L-arginine-administration. On the other hand, interval of RBCs, time to first response (TFR), and time to first peak (TFP) were significantly increased after L-arginine-administration. Basal pressure was decreased even if after vehicle-administration.

14 single afferent fibers (Aδ-fibers: n=7, CV: 6.45 ± 1.21 m/sec, C-fibers: n=7, CV: 1.56 ± 0.17 m/sec) were isolated. In both Aδ- and C-fiber SAAs, the peak of firing rate (FR) of SAAs and FR/bladder pressure values during RBCs and FR during the non-contractile phase were decreased. Interval and TFP were increased significantly after L-arginine-administration, which were more remarkable in Aδ-fibers than C-fibers (Table 1).

Interpretation of results

The present study demonstrates that both mechanosensitive Aδ- and C-fibers responsive to bladder distension are also responsive to bladder contractions. After L-arginine-administration, the amplitude of RBCs did not change whereas RBCs disappeared for a while reflected as the increases in TFR and TFP, suggesting that L-arginine can inhibit the afferent pathway from the bladder, but not the efferent pathway. Moreover, the significant decrease in the peak of FR after L-arginine-administration further supports its selective action on the afferent pathway. These findings may give us a new insight into the possible mechanism action of L-arginine/NOS system in inhabiting detrusor overactivity (DO) and overactive bladder syndrome (OAB) since microcontractions are speculated to be responsible for development of DO and OAB (2).

Concluding message

The present results indicate that mechanosensitive afferent activities of both Aδ- and C- fibers of the rat bladder are capable of being responsive to both stretch and contractile stimuli. They also suggest that the increased production of endogenous NO, caused by L-arginine-administration, can inhibit the activation of mechanosensitive afferent nerves induced by bladder contractions. To our knowledge, this is the first direct demonstration of the inhibitory action of L-arginine on SAAs during bladder “contractions”.

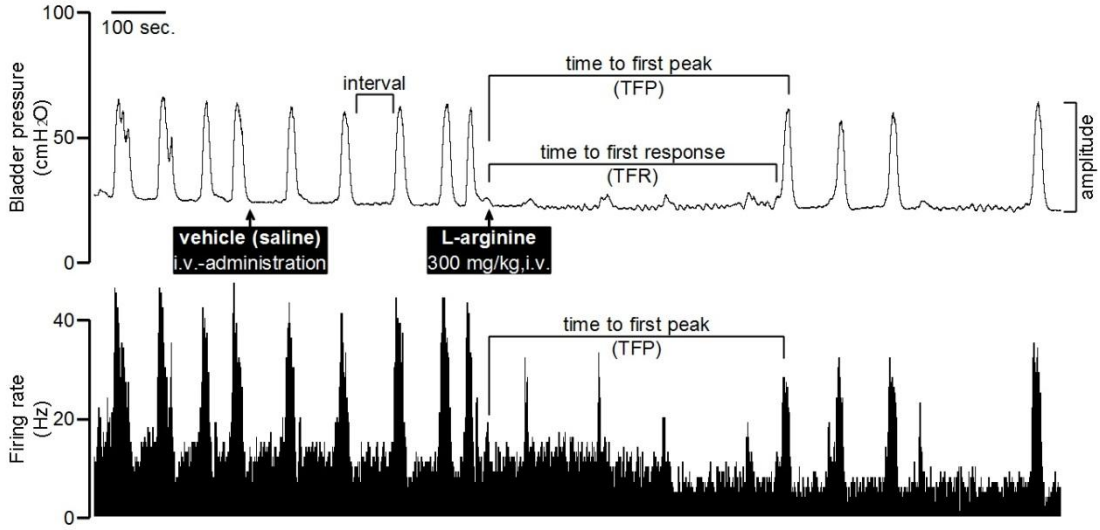

Figure 1. Typical bladder pressure (upper tracing) and firing rate of C-fiber afferent activity (lower tracing) during RBCs before and after vehicle- and L-arginine-administration.
In addition, several parameters were indicated.

Table 1. All parameters of bladder pressure and Aδ- and C-fibers afferent activities before and after vehicle- and L-arginine-administration intravenously.

bladder pressure (n=9)	**base**	**vehicle**	**L-arginine**
Amplitude (cmH_2O)	41.87 ± 2.20	43.16 ± 2.38	42.92 ± 2.42
Duration of contraction (sec.)	22.87 ± 1.98	21.47 ± 1.22	21.94 ± 1.95
Interval (sec.)	28.15 ± 3.10	41.70 ± 7.78	64.85 ± 15.33*
Basal pressure (cmH_2O)	22.04 ± 2.89	18.97 ± 2.20*	17.15 ± 1.89**
TFR (sec.)	-	82.67 ± 12.71	684.89 ± 148.54$^{\#\#}$
TFP (sec.)	-	91.44 ± 13.35	725.44 ± 137.79$^{\#\#}$
Aδ-fibers (n=7)	**base**	**vehicle**	**L-arginine**
Peak of FR during RBCs (Hz)	31.54 ± 4.22	29.61 ± 4.25	23.46 ± 4.38**,$^{\#\#}$
Interval (peak to peak, sec.)	47.50 ± 4.35	61.86 ± 9.01	109.71 ± 24.20*
FR during non-contractile phase (Hz)	5.13 ± 1.94	3.95 ± 1.51	2.64 ± 1.19**
FR/bladder pressure during RBCs (Hz/cmH_2O)	0.30 ± 0.05	0.30 ± 0.05	0.23 ± 0.06*,$^{\#\#}$
TFP (sec.)	-	95.14 ± 16.26	625.14 ± 175.72$^{\#}$
C-fibers (n=7)	**base**	**vehicle**	**L-arginine**
Peak of FR during RBCs (Hz)	31.64 ± 8.31	29.71 ± 7.84	24.43 ± 6.96*
Interval (peak to peak, sec.)	52.00 ± 4.05	65.48 ± 9.44	83.95 ± 13.95*
FR during non-contractile phase (Hz)	4.27 ± 1.67	3.47 ± 1.48	2.31 ± 0.87*
FR/bladder pressure during RBCs (Hz/cmH_2O)	0.32 ± 0.09	0.30 ± 0.09	0.26 ± 0.07
TFP (sec.)	-	102.86 ± 13.41	860.29 ± 138.86$^{\#\#}$

Values are indicated as mean ± S.E.M. FR: firing rate of afferent activity. TFR: time to first response. TFP: time to first peak. *P<0.05, **P<0.01: significant differences from base. $^{\#}P$<0.05, $^{\#\#}P$<0.01: significant differences from vehicle.

References

1. Eur Urol 2010; Oct 26 (E-pub)
2. Am J Physiol Renal Physiol 2007; 292(3): F1065-72
3. J Neurophysiol 1994; 72: 2420

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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	**Animal Ethics Committee, The University of Tokyo Graduate School of Medicine**