

THE IMPACT OF DAI-KEN-CHU-TOU ON COLD-STRESS INDUCED DETRUSOR OVERACTIVITY AND NEUROLOGICAL RECEPTORS IN THE BLADDER

Hypothesis / aims of study

Cold stress produced by sudden change or continuous exposure to low temperature exacerbates lower urinary tract symptoms (LUTS), such as urinary urgency, frequency, and nocturia. Stimulation of C-fibers in the bladder and TRPM8 channels in the skin have been reported as mechanisms of cold stress related LUTS. Dai-ken-chu-tou (DKT), a chinese herbal medicine has been traditionally used for improvement of bowel conditions and is now paid attention in recovery of LUTS. Compared with anticholinergics, DKT has many efficacies and very little side effects. In basic research, DKT is known to influence intestinal tracts by stimulating the pathway of TRPV1 and TRPA1 by increasing adrenomedulin. Stimulation of the TRPV1 has been proven to increase bladder stimulation and seems to worsen frequency. However, in treatment of LUTS, reports that DKT improve frequency and sensitivity to cold exist, but the mechanism is still not understood. We examined whether DKT improves cold stress related LUTS in rats and discussed the mechanism of DKT against frequency induced by cold stress.

Study design, materials and methods

Ten-week-old female Sprague-Dawley rats (n=22, 230-290g) were used for the experiment. The rats were randomly divided into 2 groups, which were kept with DKT including food (2700mg/kg) or normal food for 4 weeks. After 4 weeks, the rats were anesthetized (sevoflurane 3%) and the urinary bladder was exposed, incised at the center of the dome. A polyethylene catheter was inserted and the free end was tunneled subcutaneously and exteriorized at the back of the neck. Three days after cannulation, the rats underwent cystometry (CMG) unanesthetized. CMG was first performed in room temperature (RT, median 25 celsius) for 20 minutes. Rats were then put into low temperature (LT, median 4 celsius) for 20 minutes. After LT, rats were put into RT again for 20 minutes. Basal pressure and micturition pressure of the bladder were measured. Micturition volume and voiding interval were measured to see the change rate between RT and LT. After CMG, the whole bladder was removed and real time PCR was performed to see the effect of DKT against neuromechanism in the bladder. Immunohistochemistry was also performed to confirm the expression of neurochemical receptors in the bladder.

Results

Basal pressure and micturition pressure did not show a difference between control rats and DKT rats, but voiding interval and micturition volume showed a significant improvement in DKT rats. The change rate of voiding interval and micturition volume when exposed to cold stress showed a significant decrease in DKT rats (Table 1, Fig 1). Results of real time PCR of the bladder are shown in Fig 2. Down regulation of P2X3, TRPV1, and TRPM8 was seen in DKT rats. Neurotransmitter materials such as substance P (SP), neurokinin A (NKA) and B (NKB) did not show any difference between both groups. Immunohistochemistry showed decrease of P2X3 and TRPV1 in DKT rats (Fig 3, 4).

Table1

	RT			LT		
	control	DKT	p value	control	DKT	p value
basal pressure (mmHg)	22.1	19.4	N.S	31.1	23.2	N.S
micturition pressure (mmHg)	87.6	96.1	N.S	95.6	84.9	N.S
voiding interval (min)	5.1	4.8	N.S	2.1	2.8	p<0.05
micturition volume (ml)	7.8	7.7	N.S	4	5.8	p<0.05

change rate in cold stress

	control	DKT	p value
voiding interval	0.5645	0.3563	p<0.05
micturition volume	0.4399	0.221	p<0.05

Fig 1

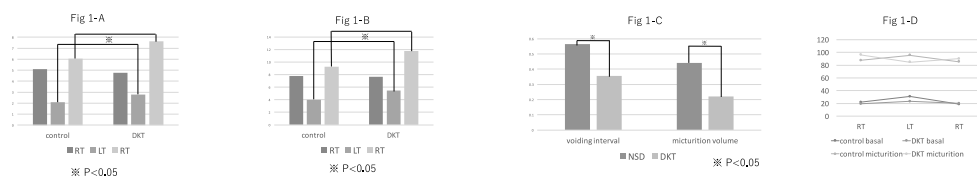


Fig1-A: voiding interval. Fig 1-B: micturition volume. Fig 1-C: change rate with cold stress. Fig 1-D: bladder pressure.

Fig 2

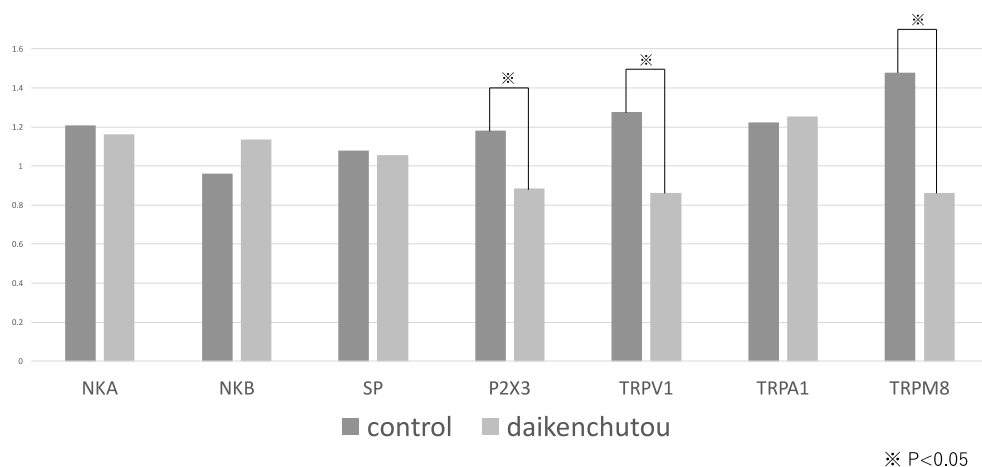


Fig 3

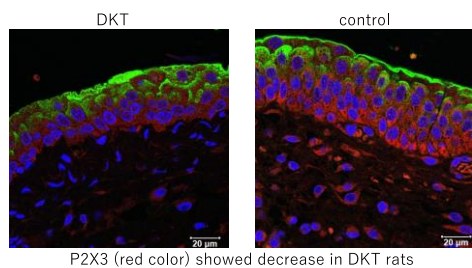
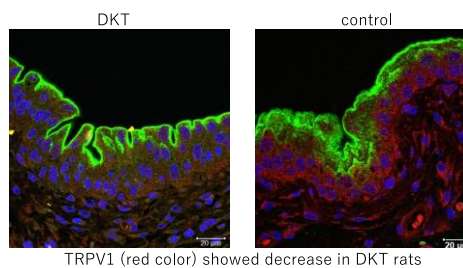


Fig 4



Interpretation of results

From this study, DKT showed a significant improvement with cold stress induced LUTS in rats without changing voiding pressure and patterns. The mechanism of this improvement may be explained by the down regulation of the c-fiber receptors such as TRPV1. Down regulation of such receptors may mean that DKT down regulates stimulation of the c-fiber activated LUTS and may be a reasonable treatment against other symptoms such as overactive bladder.

Concluding message

DKT improved cold stress related frequency in rats. Down regulation of P2X3, TRPV1 and TRPM8 may have a relation with the improvement in cold stress related frequency in rats. DKT seems to be a reasonable treatment against cold stress induced LUTS.

References

1. T.Minagawa et al. Int J Urol. 2015, 22 (3): 254-263
2. T.Kono et al. J Crohns Colitis. 2010, 4 (2), 161-170

Disclosures

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