

- 26 Zvarova K, Vizzard MA. Distribution and fate of cocaine- and amphetamine-regulated transcript peptide (CARTp)-expressing cells in rat urinary bladder: a developmental study. *J. Comp. Neurol.* 2005; **5**: 501–17.
- 27 Rajaofetra N, Passagia JG, Marlier K *et al.* Serotonergic, noradrenergic, and petidergic innervation of Onuf's nucleus of normal and transected spinal cords of baboons (*Papio papio*). *J. Comp. Neurol.* 1992; **318**: 1–17.
- 28 Thor KB. Serotonin and norepinephrine involvement in efferent pathways to the urethral rhabdosphincter: implications for treating stress urinary incontinence. *Urology* 2003; **62**: 3–9.
- 29 Kaiho Y, Kamo I, Chancellor MB *et al.* Role of noradrenergic pathways in sneeze-induced urethral continence reflex in rats. *Am. J. Physiol. Renal. Physiol.* 2007; **292**: F639–46.
- 30 Kamo I, Torimoto K, Chancellor MB *et al.* Urethral closure mechanisms under sneeze-induced stress condition in rats: a new animal model for evaluation of stress urinary incontinence. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2003; **285**: R356–65.

## Editorial Comment

### Editorial Comment from Dr Saito and Dr Shimizu to Propiverine increases urethral wall catecholamine levels and bladder leak point pressure in rats

Many reports have shown that muscarinic receptor antagonists have been used and are thought to be effective against overactive bladder, but not for stress urinary incontinence (SUI).<sup>1</sup> In Japan, only clenbuterol hydrochloride, a selective  $\beta_2$ -adrenergic agonist, is available to prescribe for SUI patients.<sup>2,3</sup> In addition, tricyclic antidepressants, such as imipramine hydrochloride, are also used for off-label use.<sup>4</sup> Interestingly, previous manuscripts have reported the efficacy of propiverine, an anticholinergic drug with calcium antagonistic action, against pure SUI patients in Japan.<sup>5</sup> In the present study, Nishijima *et al.* tried to investigate the mechanism through which propiverine is effective for treating SUI.<sup>6</sup> The authors found that intravenous injection of propiverine increased the leak point pressure in rats with vaginal distention. The mechanism of this effect could be that propiverine acted like a noradrenaline re-uptake inhibitor, and subsequently increased noradrenaline and/or dopamine levels in the plasma, cerebrospinal fluid, and urethral wall perfusion fluid. The authors concluded that the inhibition of noradrenaline re-uptake by propiverine mainly occurs at the urethral level, and partially at the central nervous system; furthermore, it might stimulate the smooth muscles of the bladder neck and proximal urethra through  $\alpha_1$ -adrenergic receptors, as well as it might stimulate the striated muscles of the urethra and pelvic floor by an activation of the spinal motoneurons. These data clearly suggest a new mechanism for the protective effect of propiverine in the lower urinary tract in the rat. A limitation of this study was whether their new finding; that is, propiverine's action as a noradrenaline re-uptake inhibitor, can be

applied to humans in clinically used-doses, considering that it is quite difficult to confirm the new finding in humans.

Motoaki Saito M.D., Ph.D. and Shogo Shimizu Ph.D.  
*Department of Pharmacology, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan*  
saitomo@kochi-u.ac.jp

DOI: 10.1111/iju.13000

## Conflict of interest

None declared.

## References

- 1 Yamaguchi O. Latest treatment for lower urinary tract dysfunction: therapeutic agents and mechanism of action. *Int. J. Urol.* 2013; **20**: 28–39.
- 2 Tsakiris P, de la Rosette JJ, Michel MC, Oelke M. Pharmacologic treatment of male stress urinary incontinence: systematic review of the literature and levels of evidence. *Eur. Urol.* 2008; **53**: 53–9.
- 3 Ushiroyama T, Ikeda A, Ueki M. Clinical efficacy of clenbuterol and propiverine in menopausal women with urinary incontinence: improvement in quality of life. *J. Med.* 2000; **31**: 311–9.
- 4 Lin HH, Sheu BC, Lo MC *et al.* Comparison of treatment outcomes for imipramine for female genuine stress incontinence. *Br. J. Obstet. Gynaecol.* 1999; **106**: 1089–92.
- 5 Sugaya K, Sekiguchi Y, Satoh T *et al.* Effect of propiverine hydrochloride on stress urinary incontinence. *Int. J. Urol.* 2014; **21**: 1022–5.
- 6 Nishijima S, Sugaya K, Kadekawa K, Ashitomi K, Ueda T, Yamamoto H. Propiverine increases urethral wall catecholamine levels and bladder leak point pressure in rats. *Int. J. Urol.* 2016; **23**: 93–9.

## Editorial Comment

### Editorial Comment from Dr Negoro to Propiverine increases urethral wall catecholamine levels and bladder leak point pressure in rats

The article by Nishijima *et al.* showed that propiverine, known as an antimuscarinic and Ca-antagonistic agent, increased leak point pressure in rats by acting as a noradrenaline re-uptake inhibitor like imipramine and nisoxetine, which mainly occurred in the urethra through  $\alpha_1$ -adrenoceptor.<sup>1</sup> Elucidating the pharmacological action of propiverine on stress urinary incontinence is appreciated, as treating stress

urinary incontinence pharmacologically is not straightforward, especially in patients suffering after radical prostatectomy, and progress in this field has been awaited.

This basic research is important to support the clinical effect of propiverine on stress urinary incontinence in a human study, though there are some points to be carefully considered, because differences in the pharmacological effect