were observed in rats and humans.[2] First, relatively high doses of propiverine as 3 mg/kg i.v. and 5 mg/kg p.o. were required to induce a noradrenaline re-uptake effect in rats, and almost no effect was observed at 1 mg/kg i.v. The maximum human dose of propiverine is 40 mg/day, which is much less than that of rats used here. The high dose required in rats is compatible with table 1 of this report showing the much weaker effect of propiverine than that of nisoxetine. Second, an increase of plasma catecholamine levels by propiverine was observed in the present study. The authors speculated that it was from leakage of catecholamines from the peripheral organs, including the urethra, in addition to from the adrenal glands, though it was not observed in the human study.[2] On this point, the authors guessed that propiverine administration can also increase the catecholamine level in the urethral wall elderly people, but its level seems not to influence the plasma catecholamine level. It would be expected that differences between young and old subjects in addition to those of different species would be evaluated, as various effects of propiverine have been reported in different conditions.[3–5] Further research will help to answer whether the administration of a physiological dose of propiverine in elderly patients actually has an inhibitory effect of noradrenalin re-uptake and increases catecholamine in the urethral wall.

The authors did not discuss the structure of propiverine that can work as a noradrenalin re-uptake inhibitor, but it might be interesting to focus on this, and to evaluate its metabolites or create new drugs that are expected to have a higher affinity in the urethral wall to increase the effect on stress urinary incontinence and reduce the side-effects.

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Conflict of interest

None declared.

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Editorial Comment

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

The prevalence of stress urinary incontinence (SUI) increases with age as well as with several factors including living habits, surgery and vaginal delivery, especially in women.[1] For the pharmacotherapy of SUI, there has been little success in the development of agents, whereas duloxetine, a serotonin-noradrenaline reuptake inhibitor, has shown clinical efficacy and has been approved in Europe, but there are concerns regarding liver toxicity and suicidal events.[2] Regarding the mechanism and site of action, duloxetine inhibits serotonin–noradrenaline re-uptake in the central nervous system ("Onuf's nucleus" in the sacral spinal cord), and thereby it has been proposed that this mechanism increases the rhabdosphincter tone and contractility through the central stimulation of pudendal motor neuron α1-adrenergic and 5-HT_2 receptors.[3]

The current study by Nishijima *et al.* has explored the possible treatment option of propiverine, an anticholinergic agent, for SUI.[4] They showed that: (i) intravenous propiverine and duloxetine increased the leak point pressure (LPP) in rats with vaginal distention; (ii) intrathecal naftopidil, an $\alpha 1_{A/D}$-adrenergic antagonist, decreased the LPP, whereas subsequent intravenous propiverine restored the LPP; (iii) propiverine showed an inhibition of the noradrenaline re-uptake; and (iv) noradrenaline and dopamine levels in the plasma and urethral wall were increased by oral propiverine supplementation (5 mg/mL/day for 10 days). These findings were consistent with their previous report that propiverine supplementation (5 mg/mL/day for 2 weeks) increased the urethral baseline pressure, whereas imidafenacin (an anticholinergic agent, 0.01 mg/mL/day) did not show such an increased response.[5] Regarding the mechanism and site of action of propiverine based on the current and previous results, it is conceivable that an increase of noradrenaline induced by propiverine can activate both sympathetic pathways and Onuf's nucleus through α1-adrenergic receptors to increase the urethral baseline pressure and LPP. These mechanisms might be reasonable to ameliorate SUI, and propiverine could be a promising tool for the treatment of SUI.

As harmonized with these basic findings, propiverine has been proven to clinically improve SUI without serious adverse events, which was also shown by the same group.[6] However, this previous clinical study showed no elevation of blood catecholamine at 8 weeks after propiverine treatment. Therefore, evidence of propiverine as an inhibitor of nora-

drenaline reuptake on urethral function is now still questionable. In addition, one of the limitations of the current study was that higher doses of propiverine were used compared with the clinical human dose. A further study with a lower dose of propiverine might be required to investigate the detailed mechanisms of propiverine on urethral function.

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