488

Kitta T[1], Miyazato M[2], Chancellor M[3], Nonomura K[4], Yoshimura N[1]
1. *Department of Urology, University of Pittsburgh School of Medicine,* ***2.*** *Department of Organ-Oriented Medicine, Faculty of Medicine, University of the Ryukyus,* ***3.*** *William Beaumont Hospital,* ***4.*** *Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University*

ALPHA2-ADRENERGIC RECEPTOR BLOCKADE POTENTIATES THE EFFECT OF DULOXETINE, A NOREPINEPHRINE AND SEROTONIN REUPTAKE INHIBITOR, ON SNEEZE-INDUCED URETHRAL CONTINENCE REFLEX IN RATS

Hypothesis / aims of study

Serotonin and norepinephrine reuptake inhibitors (SNRI) such as duloxetine have demonstrated clinical efficacy in the treatment of stress urinary incontinence (SUI). However, the therapeutic dose of duloxetine is often associated with unwanted side effects such as nausea, constipation, dizziness and fatigue. We previously reported that urethral sphincter reflexes can be inhibited by activation of alpha2 adrenoceptors (AR). Therefore, we investigated whether low-dose SNRI (duloxetine) and an alpha2 AR antagonist (idazoxan) have synergistic effects on the sneeze-induced continence reflex in rat.

Study design, materials and methods

Normal female rats and rats with SUI induced by vaginal distension (VD) were used. In VD rats, the vagina was distended with 4 ml balloon catheter for 3 hours 4 days before the experiments. Sneeze was induced by a rat's whisker cut and inserted into the nostril. (1) In normal rats, urethral responses were measured using a microtip transducer catheter inserted to the middle urethra from the urethral orifice. The effect of low-dose duloxetine (0.1 mg/kg; intravenous application [i.v.]), idazoxan (4 nmol; intrathecal application [i.t.]) or sequential administration of two drugs on the amplitude of urethral responses during sneezing (A-URS) as well as urethral baseline pressure (UBP) was evaluated. (2) In VD rats, sneeze-induced leak point pressure (S-LPP) measurements were performed before and after administration of each drug.

Results

(1) In normal rats, no parameters were changed after idazoxan (i.t.) administration alone. Low- dose duloxetine (i.v.) increased UBP by 10.3% compared with predrug values (P<0.05), but did not alter A-URS significantly. However, when low-dose duloxetine (i.v.) and idazoxan (i.t.) were co-applied, A-URS was increased by 93.9% (P<0.01) and 60.8% (P<0.05) compared with predrug values and those after low-dose duloxetine alone, respectively (Fig.1 and Fig.2a and 2b). (2) In all seven VD rats, leakage was observed during sneezing before drug administration. S-LPP of these VD rats averaged 38.7 ± 1.6 cmH2O. After low-dose duloxetine administration, fluid leakage was still observed during sneezing; however, after co-administration of low-dose duloxetine and idazoxan, fluid leakage during sneezing disappeared in two of seven incontinent VD rats, and S-LPP was significantly increased to 78.5 ± 6.0 cmH2O (P<0.01) in the remaining five incontinent VD rats (Fig.2c).

Fig.1

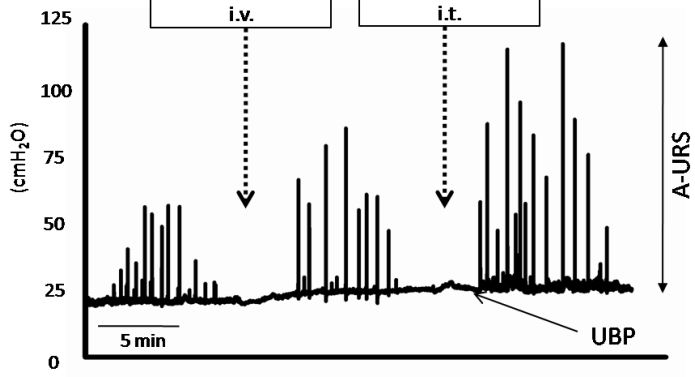
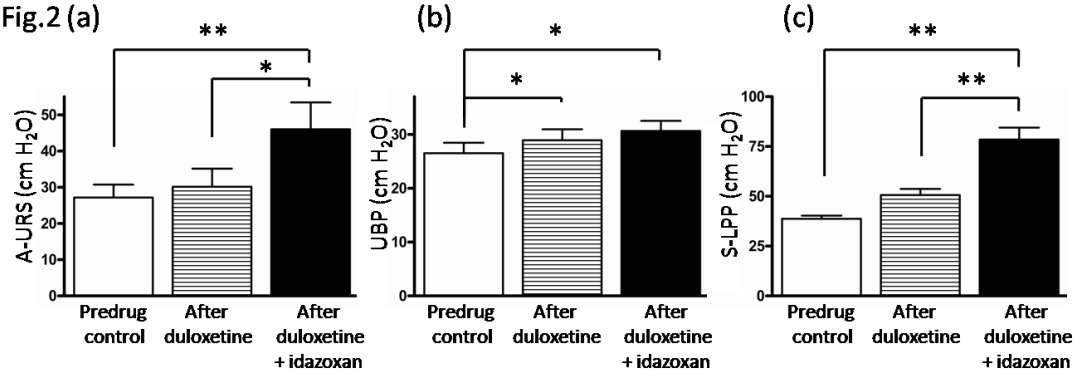


Fig.2 (a) (b) (c)



* P<0.05, **P<0.01

Interpretation of results

As hypothesized, co-administration of the alpha2 AR antagonist can enhance the anti-incontinence effects of SNRI medications. Low-dose duloxetine did not alter A-URS or S-LPP significantly, by it self, but after additional administration of idazoxan enhanced A-URS and S-LPP. The enhancing effects of co-applied duloxetine (low dose) and idazoxan on A-URS was comparable to those

previously observed in rats treated with high-dose (1 mg/kg) duloxetine [1]. It has been shown that increased UBP after duloxetine is due to activation of sympathetic pathways carried through the hypogastric nerves, which innervate urethral smooth muscles [1] and that an active, neurally mediated mechanism to induce striated muscle contractions of the external urethral sphincter (as represented by A-URS) is crucial for preventing urinary leakage during sneeze-induced continence mechanism [2]. Therefore, the strategy focusing on enhancing A-URS rather than UBP might be preferable for the treatment of SUI under suddenly occurring stress conditions such as sneezing.

Concluding message

These results indicate that the effects of duloxetine are enhanced by alpha2 AR blockade. Thus, co-administration with alpha2 AR antagonists could reduce the effective dosage and might decrease unwanted side effects of SNRI agents. The present findings therefore support the concept that the combination therapy with alpha2 AR antagonists may provide an effective and novel strategy to reinforce the clinical efficacy of SNRI agents in the treatment of SUI.

References

1. Am J Physiol Regul Integr Comp Physiol (2008) 295, R264-72
2. Am J Physiol Regul Integr Comp Physiol (2003) 285, R356-65

Specify source of funding or grant	**NIH DK067226, AR049398 and DK055387**
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	**University of Pittsburgh Institutional Animal Care and Use Committee**