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EFFECT OF SINGLE OR CO-ADMINISTRATION OF DULOXETINE AND ROBALZOTAN ON VOLUME-INDUCED BLADDER CONTRACTION IN URETHANE-ANESTHETIZED RATS

Hypothesis / aims of study

Serotonergic raphe neurons play an important role in the micturition reflex by regulating Onuf's and sacral parasympathetic neurons (SPN). Activation of 5-HT_{1A} receptors in raphe nuclei inhibits neuronal firing and 5-HT release which is reversed by 5-HT_{1A} antagonists (1). In this study, we investigated the cystometric effect of duloxetine, a serotonin and norepinephrine (NE) reuptake inhibitor (SNRI) and robalzotan, a 5-HT_{1A} antagonist on refill volume-induced bladder contraction (VIBC) in urethane-anesthetized rats and evaluated the effect of co-administration of the compounds.

Study design, materials and methods

The urinary bladders of female SD rats were cannulated via the dome and the urethra was ligated around the orifice. One hour post surgery, VIBC was performed with saline infusion (0.1 ml/min). Once the micturition reflex is initiated and bladder was contracted for 5-7 times the infusion rate was reduced to 0.005 ml/min and VIBC was maintained for 20 min. Bladder was then drained and 30 min later bladder was refilled as above. Test compound or vehicle was administered intravenously at the third or fourth refill and VIBC was measured.

Results

Bladders infused with saline evokes a reproducible rhythmic VIBC. Robalzotan (0.0001-0.1 mg/kg, iv) produced an inhibitory effect with a complete inhibition of bladder contraction at 0.01-0.1 mg/kg, iv (Fig 1A & Fig 2A). The time of inhibition by robalzotan at 0.01 mg/kg, iv was 5.84 ± 1.3 min, which was completely blocked by 8-OH-DPAT (0.1 mg/kg, iv). Duloxetine (10-30 mg/kg, iv) produced an inhibitory effect on VIBC. Both frequency and amplitude were inhibited and an elevated basal threshold of bladder contraction was observed (Fig 1B & Fig 2B). Duloxetine at 3 mg/kg did not produce significant effects on VIBC. However, with co-administration of duloxetine (3 mg/kg, iv) and robalzotan (0.01 mg/kg, iv), VIBC inhibition was markedly augmented from 5.84 ± 1.3 min (robalzotan alone) to 28.0 ± 9.4 min (Fig 2C).

Fig 1

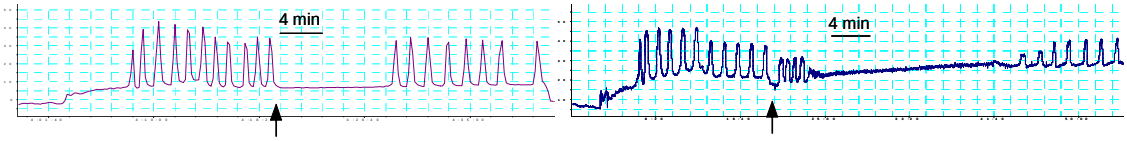

Fig 1. VIBC trace showing bladder pressure (mmHg) and bladder contractions prior to and after administration of robalzotan 0.1 mg/kg, iv (A) and duloxetine 30 mg/kg, iv (B). Arrow: dosing.

Fig 2.

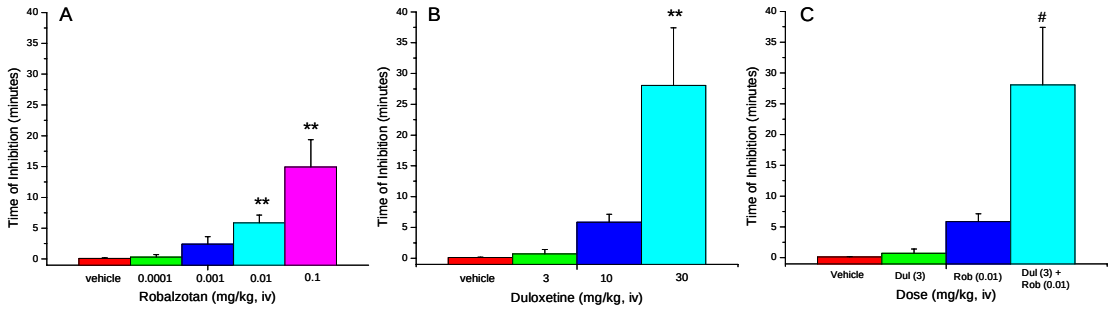

Fig 2. Effect of robalzotan, duloxetine and co-administration of both compounds on refill VIBC. (A) Dose-dependent effect of robalzotan (0.0001-0.1 mg/kg, iv, n = 5-14); (B) Dose-dependent effect of duloxetine (1-30 mg/kg, iv, n = 5-8); (C) Co-administration of robalzotan 0.01 mg/kg, iv and duloxetine 3 mg/kg, iv (n =10) in anesthetized rats. ** $p<0.01$ from vehicle; # $p<0.05$ from robalzotan (0.01 mgkg, iv).

Interpretation of results

Duloxetine has been shown to be efficacious for the treatment of depression and stress urinary incontinence. While the exact mechanism of action for monoamine reuptake inhibitors is not known, it is clear that their chronic administration leads to an increase in the raphe neuronal firing rate and to desensitization of the 5-HT_{1A} autoreceptor (2). The raphe nuclei project to Onuf's nucleus and the SPN and both these areas and the sacral dorsal horn express various 5-HT receptor subtypes. Activation of the 5-HT_{1A} autoreceptors inhibits raphe firing and 5-HT release and increases the micturition reflex. 5-HT_{1A} antagonists such as WAY100635 and robalzotan block this effect (3). We evaluated whether simultaneous increases in monoamine levels produced by duloxetine in the presence of an autoreceptor antagonist would potentiate the inhibition of the micturition reflex. Taken together, our results demonstrate that co-administration of duloxetine and robalzotan did potentiate inhibition of the micturition reflex and that this approach led to synergistic effects for this pathway. While not directly investigated here, duloxetine also increases levels of NE in pontomedullar noradrenergic neurons and peripheral nerves, which may also play a role in the inhibition of the micturition reflex and in maintaining urethral sphincter tone.

Concluding message

The SNRI duloxetine and 5-HT_{1A} antagonist robalzotan produced inhibitory effects on refill VIBC in a dose-dependent manner in urethane-anesthetized rats. The inhibitory effect is potentiated with co-administration of both compounds. These *in vivo* results indicate that the blockade of 5-HT_{1A} somatodentritic autoreceptors may inhibit micturition reflex and that the inhibition may be potentiated by a SNRI.

References

(1) *JPET* 288: 820-826, 1999. (2) *JPET* 285: 404-412, 1998. (3) *Naunyn-Schm Arch Pharmacol* 366: 528-536, 2002.