Involvement of both β_2- and β_3-adrenoceptors in the inhibition of neurogenic contractions of mouse isolated urinary bladder

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Objectives

While it is well established that stimulation of β-adrenoceptors (β-ARs) produces urinary bladder smooth muscle relaxation, very little is known about how β-AR stimulation affects neuronally mediated bladder contractions. Relaxation of basal tension and pre-contracted urinary bladder strips has been shown to be mediated by both β_2- and β_3-ARs in rat (1) and pig (2) and by β_3-AR in dog (1), primates (3) and human (4, 5). Recently, the inhibition of EFS-induced contractions of human urinary bladder by stimulation of β_3-ARs has been demonstrated (6).

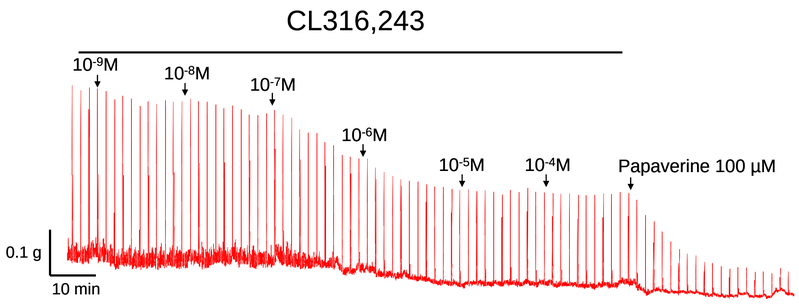
The purpose of the present study was to characterize the β-AR subtypes involved in the inhibition of neurogenic contractions of mouse urinary bladder.

Methods

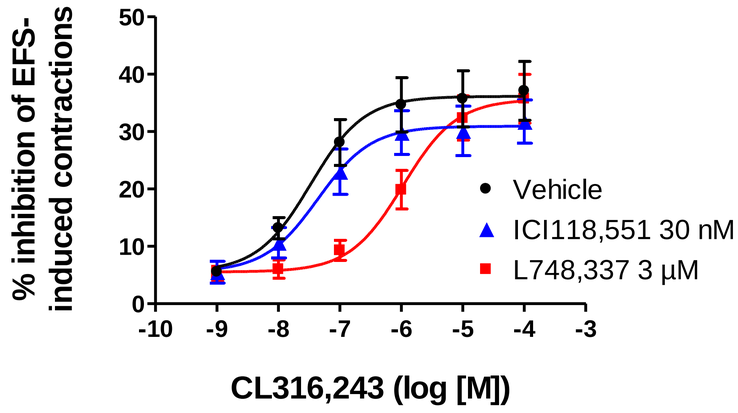
- Urinary bladders were obtained from adult female C57/Bl6 mice (aged 11-13 weeks) sacrificed by cervical dislocation.
- Bladders were bisected and bladder halves mounted into 5 mL organ baths under 0.5 g of initial tension in the presence of prazosin (1 µM) in order to block α_1-ARs.
- ICI118,551 (β_2-AR antagonist at 30 nM), L748,337 (β_3-AR antagonist at 3 or 10 µM) or vehicle (0.001% DMSO in distilled water) were added to the organ bath.
- 15 min later, tissues were subjected to EFS using the following parameters: maximal current, frequency of 2.5 Hz, pulse duration 0.3 ms, trains of pulses 2 s every minute.
- Once responses to EFS stabilized, cumulative concentration-response curves to β-AR agonists (fenoterol, a β_2-AR selective agonist; CL316,243, a β_3-AR selective agonist; isoproterenol, a non-selective β-AR agonist) were constructed.
- Results are expressed as percent inhibition of EFS-induced contractions.

Results

Effects of the selective β_3-AR agonist CL316,243 on EFS-induced contractions of mouse urinary bladder strips

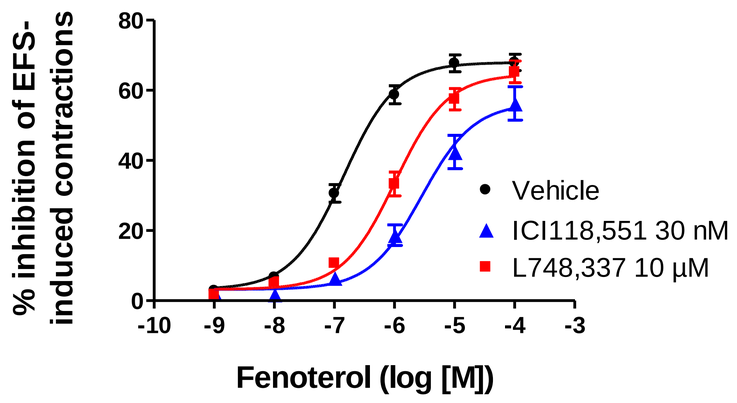


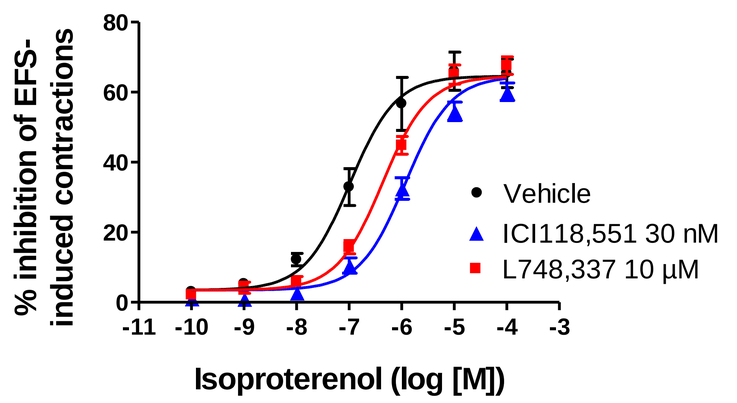
Typical recording showing the inhibitory effects of CL316,243 on EFS-induced contractions of mouse urinary bladder strips



- CL316,243 concentration-dependently inhibited EFS-induced contractions of mouse urinary bladder strips with a pEC_{50} value of 7.48 and an E_{max} value of 36 ± 5%.
- L748,337 (but not ICI118,551) significantly inhibited the effects of CL316,243 without affecting the maximal response with a pA_2 value of 7.00, that is similar to the affinity value (pK_i = 6.5) reported at rat recombinant β_3-ARs (7).

Effects of β-AR antagonists on fenoterol and isoproterenol-mediated inhibition of EFS-induced mouse urinary bladder strip contractions

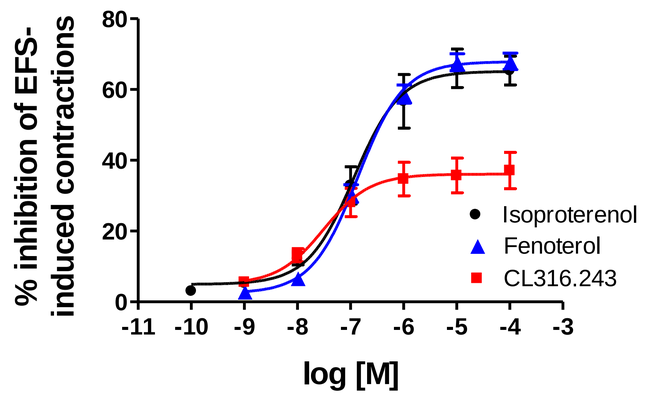




- Fenoterol and isoproterenol inhibited EFS-induced contractions of mouse urinary bladder strips in a concentration-dependent manner with a pEC_{50} and E_{max} values of 6.85 and 68 ± 2% and 6.98 and 65 ± 4%, respectively.
- ICI118,551 potently blocked the relaxing effects of fenoterol (pA_2 = 8.80) and isoproterenol (pA_2 = 8.53), values that are very similar to the pA_2 value (8.97) reported in rat isolated myometrium, a tissue known to express β_2-AR (8).
- In contrast, L748,337 inhibited the fenoterol and isoproterenol effects only at relatively high concentrations (pA_2 = 5.79 and 5.49, respectively).

Comparison of inhibitory effects of β-AR agonists on EFS-induced mouse urinary bladder strip contractions

- Both fenoterol and isoproterenol were able to inhibit EFS-induced contractions of mouse urinary bladder strips with similar potency and maximal inhibition of approximately 65%.
- CL316,243 had similar potency, but only produced a maximal inhibition of 36%.



Conclusions

The current results demonstrate that stimulation of both β_2- and β_3-ARs produces inhibition of neuronally-mediated contractions of mouse urinary bladder. CL316,243 acts exclusively through stimulation of β_3-ARs, whereas fenoterol and isoproterenol appear to activate mainly β_2-ARs. In addition, the stimulation of β_2-ARs produces a greater degree of inhibition than stimulation of β_3-ARs, suggesting a predominant role of β_2-ARs. Further studies are required to define whether the effects of β-AR stimulation on EFS-induced contractions are solely due to a post-junctional action or whether pre-junctional receptors are also involved.

References

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