

Stimulation of β_3 -adrenoceptors inhibits EFS-induced contractions of human isolated urinary bladder

N° 190

Moèz Rekik ¹, Céline Rouget ¹, Philippe Camparo ², Henry Botto ³, Philippe Lluet ¹, Timothy D Westfall ¹, Stefano Palea ¹

1. UROsphere, Faculty of Pharmaceutical Sciences, 35 Chemin des Maraîchers, Toulouse, France 2. Foch Hospital, Anatomy and Cytopathology Department, Suresnes, France 3. Foch Hospital, Urology Department, Suresnes, France

Objectives

- Activation of β -adrenoceptors (β -ARs) has been shown to produce relaxation of pre-contracted urinary bladder smooth muscle suggesting that β -AR agonism could promote relaxation of detrusor muscle during urine storage.
- β -ARs are sub-classified into β_1 , β_2 and β_3 -subtypes. The distribution of β -AR subtypes in the bladder is species dependent, however in some species, including human, the β_3 -AR subtype appears to be predominant. In human bladder this receptor has been shown to mediate relaxation of pre-contracted human detrusor strips ⁽¹⁻³⁾ suggesting that β_3 -agonists have potential for the pharmacological treatment of overactive bladder.
- A number of studies have demonstrated an effect of β -AR agonists on basal tension and pre-contracted detrusor strips, however very little is known about how β -AR agonism affects neuronal efferent activity.

The aim of the present study was to investigate the effect of β -AR agonism on neurogenic contractions of human isolated detrusor and to characterize the β -AR subtypes involved.

Methods

- Detrusor smooth muscle strips (devoid of urothelium) were obtained from 11 patients (72 \pm 3 years old, 10 male and 1 female) undergoing cystectomy due to bladder cancer.
- Strips were mounted under 1 g of initial tension and electrical field stimulation (EFS) applied using the following parameters: maximal current, frequency of 10 Hz, square pulses of 0.1 ms, trains of 5 s every min.
- L748,337 (β_3 -AR antagonist at 0.3, 1 and 3 μ M), ICI118,551 (β_2 -AR antagonist at 30 and 100 nM) or vehicle were added to the organ bath followed 20 min later by a cumulative concentration-response curve to a β -AR agonist (isoproterenol, L755,507 or CL316,243).
- Responses obtained at each concentration of agonist were expressed as percentage variation from basal EFS-induced contractions obtained before agonist addition.

Conclusions

While it is well known that stimulation of β -ARs produces relaxation of basal tension and pre-contracted strips of human isolated bladder, there are very few reports on the effect of β -AR agonists on EFS-induced responses.

Here, we clearly demonstrate that isoproterenol is able to significantly inhibit EFS-induced contractions of human detrusor through activation of β_3 -ARs, confirming a previous result ⁽⁴⁾.

References

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Results

Effects of β_3 -AR agonists on EFS-induced contractions of human urinary bladder

- Isoproterenol (10 nM to 100 μ M) inhibited TTX-sensitive EFS-induced contractions of human bladder smooth muscle strips in a concentration-dependent manner with an EC₅₀ value of 0.19 \pm 0.11 μ M and an Emax value of 66.6 \pm 3.9% at 30 μ M.

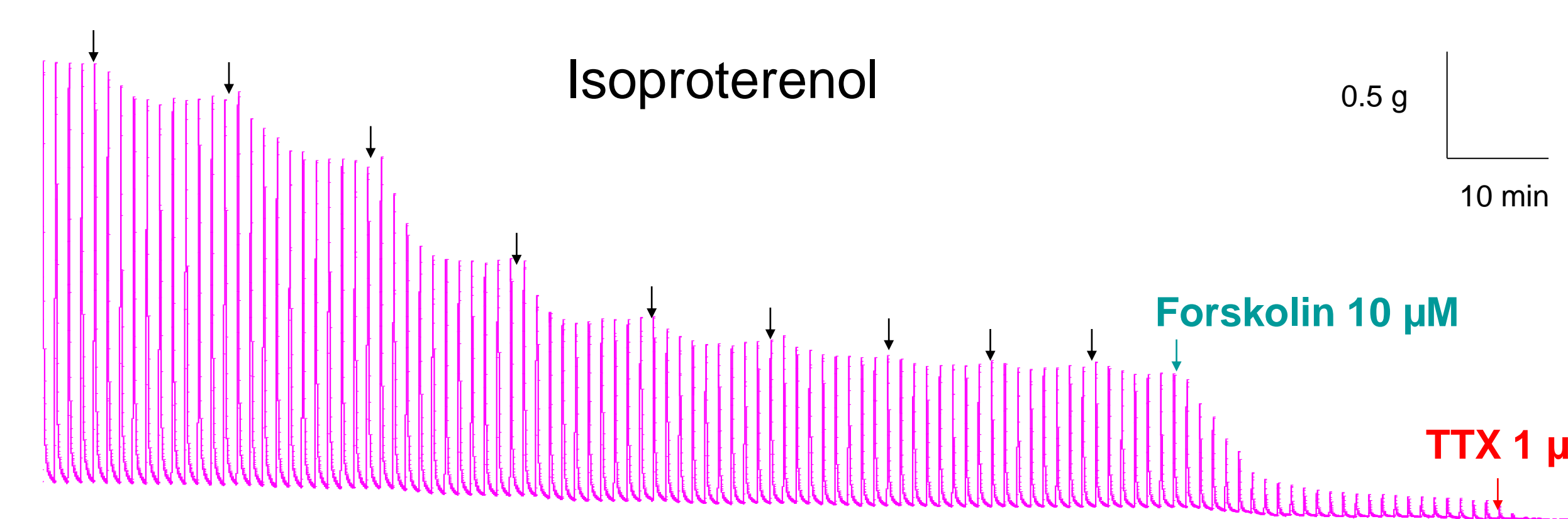


Figure 1. Typical recording showing the effects of increasing concentrations of isoproterenol (10 nM to 100 μ M) on EFS-induced contractions of isolated human bladder.

- In contrast to isoproterenol, the human β_3 -AR partial agonist L755,507 produced a potent but only a maximum inhibition of 30.0 \pm 8.9 % at 100 nM, while the rodent selective β_3 -AR CL316,243 only decreased EFS-induced contractions by 20.8 \pm 3.5 % at 10 μ M.

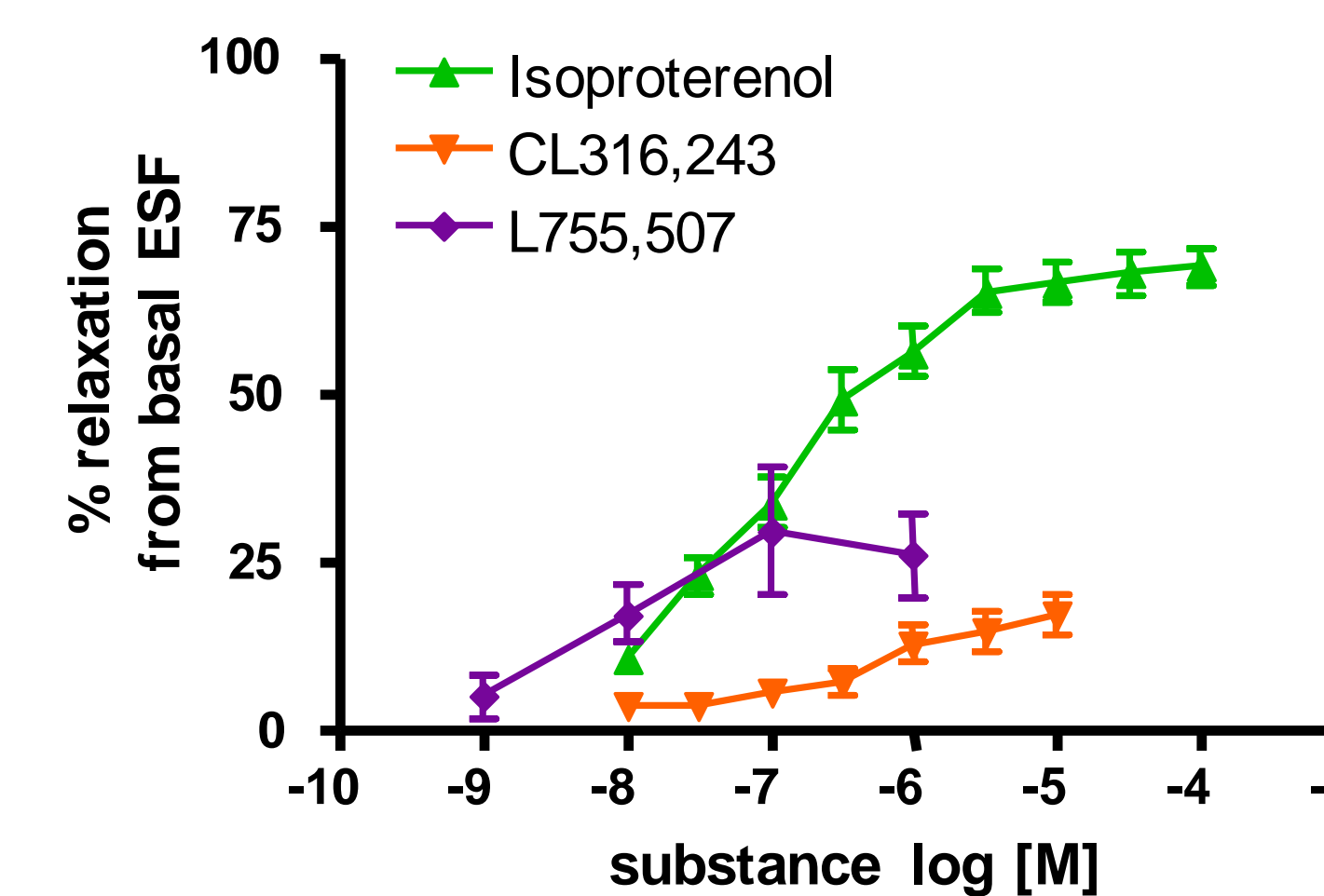


Figure 2. The effect of cumulative concentrations of isoproterenol, CL316,243 or L755,507 on EFS-induced contractions of human urinary bladder strips.

In contrast, the human β_3 -AR partial agonist L755,507 produced a potent, but only partial inhibition of EFS-responses while the rodent β_3 -AR selective agonist CL316,243 only produced a slight effect.

While clearly β_3 -AR agonism can produce relaxation of human bladder through post-junctional receptors (and therefore relaxation of basal tension during urine storage),

Effects of β_2 and β_3 -AR antagonists on isoproterenol-induced relaxation of EFS-induced contractions of human urinary bladder

- The β_2 -AR antagonist ICI118,551 (30 and 100 nM) had no effect on the response to isoproterenol.

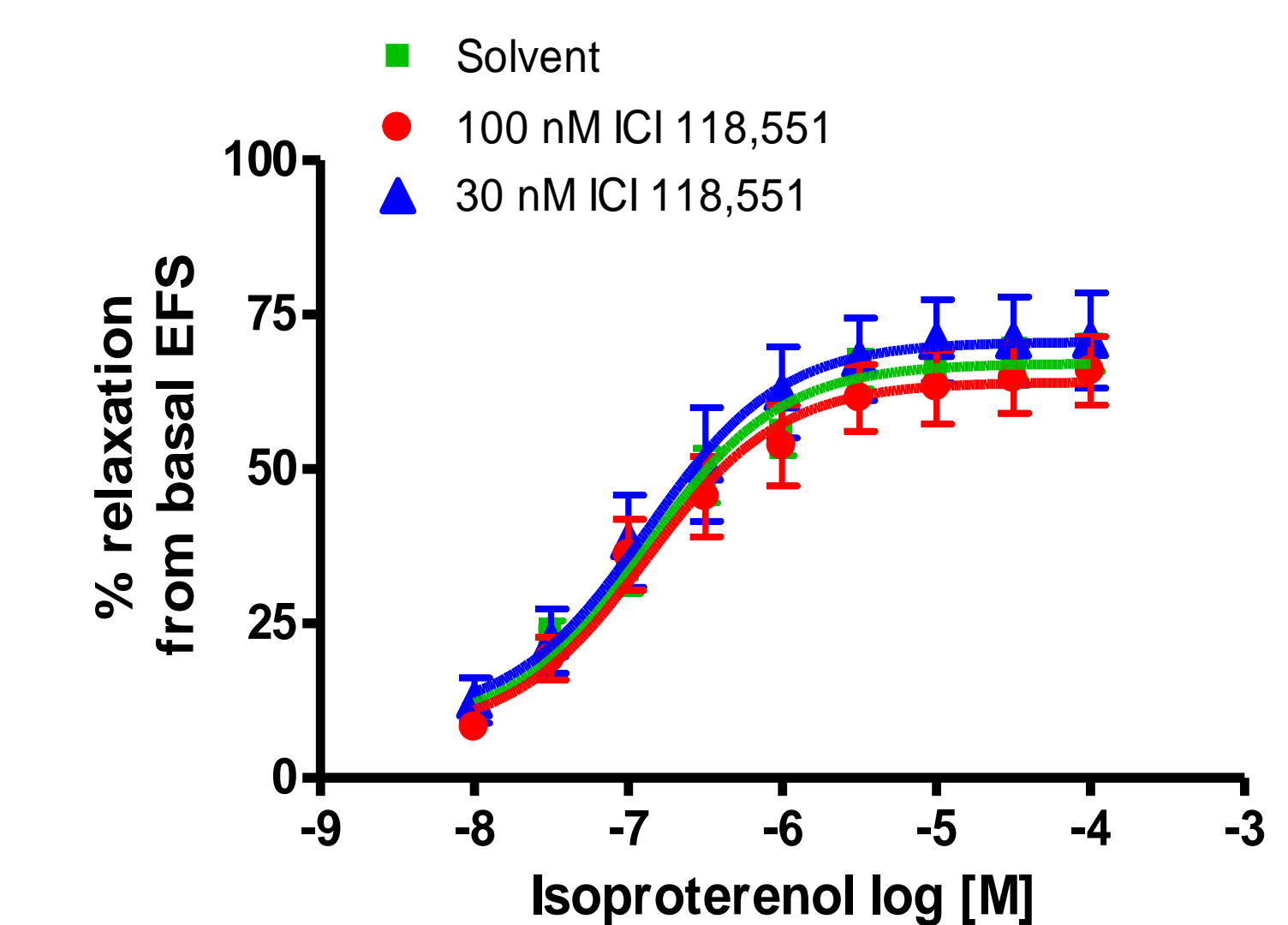


Figure 3. Cumulative concentration-response curves for isoproterenol in the absence and presence of ICI118,551 obtained in human bladder strips contracted by EFS.

- The β_3 -AR antagonist L748,337 produced a concentration-dependent rightward shift of isoproterenol-induced response curves without affecting the maximal effect. Schild plot analysis revealed a pA₂ value of 7.37 and a slope of 1.07 \pm 0.19 indicating competitive antagonism. This affinity value for L748,337 is lower than the value (8.40) reported in recombinant β_3 -AR CHO cells ⁽⁵⁾ but similar to the value (pK_B = 7.65) reported in human isolated urinary bladder precontracted with carbachol ⁽¹⁾.

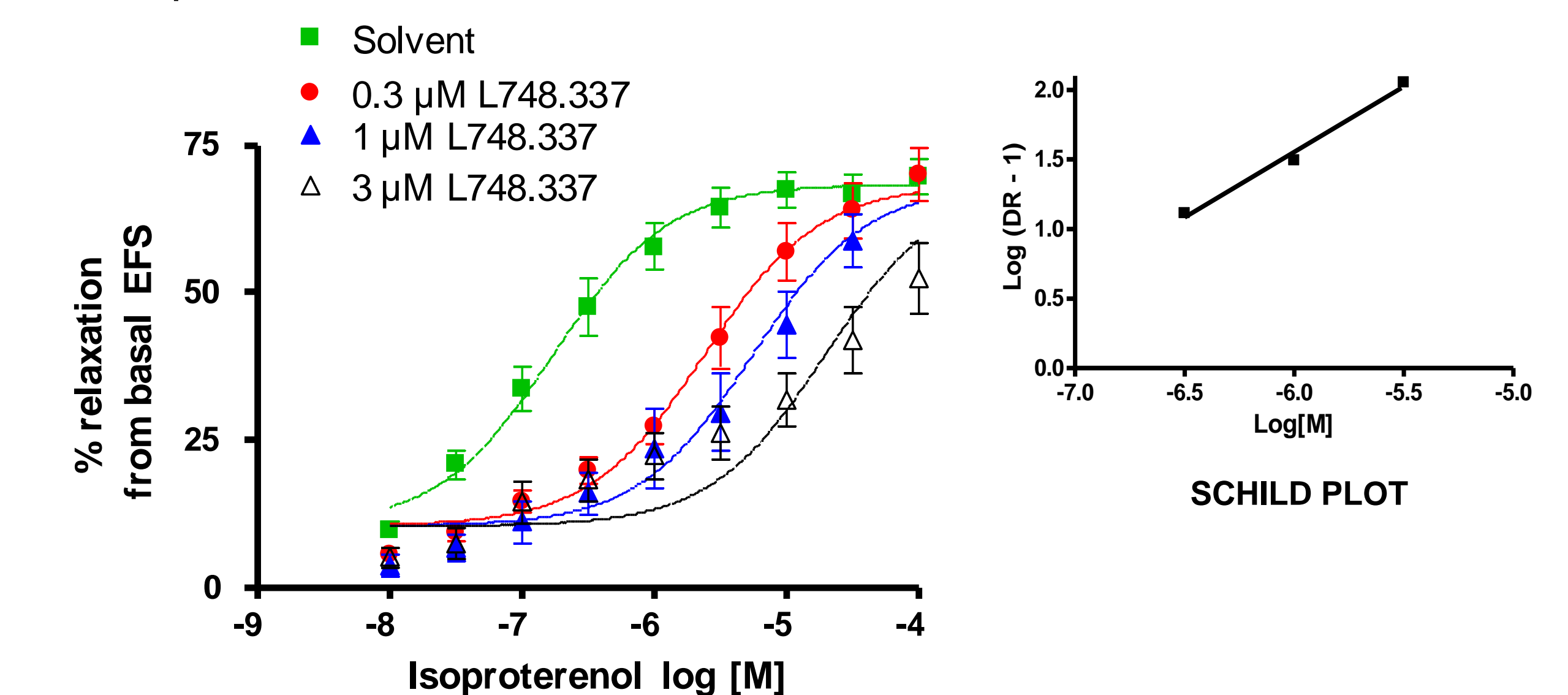


Figure 4. Cumulative concentration-response curves for isoproterenol in the absence and presence of 0.3, 1 and 3 μ M L748,337 obtained in human bladder strips contracted by EFS.

the current results may imply that β_3 -AR agonism can also inhibit neuronally mediated acetylcholine release through pre-junctional receptors and thus directly modulate neuronal contractions. Further studies are necessary to confirm this hypothesis.