

POTENTIATION OF NEUROGENIC CONTRACTIONS OF THE RAT DETRUSOR MUSCLE BY 5-CARBOXAMIDOTRYPTAMINE: INVOLVEMENT OF 5-HT₇ RECEPTOR AND ANOTHER 5-HT RECEPTOR SUBTYPE

Hypothesis / aims of study

Serotonin (5-HT) enhances the neurogenic contractile response induced by electrical field stimulation (EFS) in the rat isolated urinary bladder (1). The aim of this study was to further characterize the receptors involved in this effect by using 5-carboxamidotryptamine (5-CT), an agonist described to be selective for 5-HT_{1A} and 5-HT₇ receptors (2). The effects of selective antagonists for these receptors, namely WAY100,635 and SB-269970 (3) respectively, were also tested.

Study design, materials and methods

Detrusor muscle strips were prepared from female Wistar rats, connected to tension transducers in organ baths containing Krebs solution and, after equilibration, exposed to KCl 80 mM. After washouts, tissues were incubated with SB-269970 at 0.3 - 1 and 3 μ M, WAY-100,635 at 0.1 μ M or their solvent (distilled water). Concentration-response curves (CRC) to 5-CT were then performed after stabilization of the contractile response induced by EFS (constant current: 800 mA; pulse width: 0.1 ms; frequency: 15 Hz; trains of pulses of 4 s every 120 s). Potentiating effects were calculated as delta increase over basal contractions and expressed as % of KCl 80 mM-induced contraction.

Results

In the absence of SB-269970, 5-CT induced a biphasic concentration-dependent potentiation of neurogenic contractions. We decided to analyze the first phase of the response to 5-CT, since it was observed at relatively small concentrations of the agonist (0.1 -100 nM) and thus probably mediated by a specific receptor. The second phase, still observed in the presence of SB-269970, was not characterized since it was not possible to reach a plateau for the agonist response.

SB-269970 concentration-dependently antagonized the first phase of the response to 5-CT. The Schild plot gave a pA₂ value of 8.77 (see Figure) and a slope not significantly different from unity (0.91 \pm 0.11) indicating a competitive antagonism. WAY 100,635 at 0.1 μ M had a limited antagonistic effect on 5-CT, pEC₅₀ in the absence and presence of this antagonist being 9.30 \pm 0.14 and 8.51 \pm 0.14, respectively. By using the Furchgott method we calculated a pA₂ of 7.71 for WAY100,635.

Interpretation of results

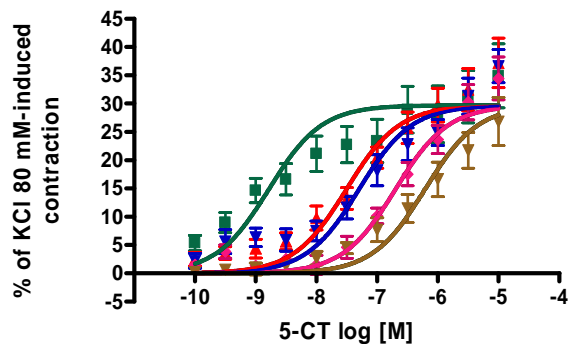
Activation of 5-HT_{1A} receptors by 5-CT seem improbable since the antagonistic potency of WAY100,635 observed in the present study (pA₂=7.71) was 100 times less than its pA₂ value previously reported on cloned 5-HT_{1A} receptors (9.71) (3). However, the present pA₂ value for SB-269970 (pA₂= 8.77) is consistent with its potency on cloned 5-HT₇ receptors (pA₂=8.5) (4). Therefore, we conclude that 5-CT potentiating effects on neurogenic contractions are mediated by 5-HT₇ receptors. The nature of the receptor mediating the response to high concentrations of 5-CT is presently unknown.

Concluding message

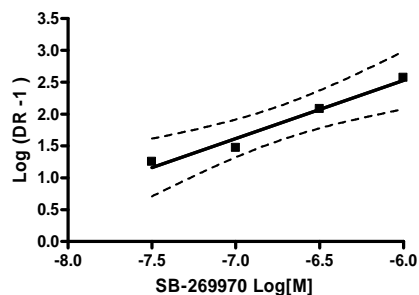
Recently, in human detrusor muscle strips, the potentiation of [³H]-acetylcholine release by 5-CT was found to be mediated by 5-HT₇ receptors (2). Therefore, this 5-HT receptor subtype may have a role in the genesis of bladder overactivity in humans. Our experimental model in the rat isolated detrusor muscle could be useful for the selection of new 5-HT₇ receptor antagonists.

References

1. BJU Int (2004) 94; 1125-1131.
2. J Pharmacol Exp Ther (2006) 316; 129-35.
3. Br J Pharmacol (2000) 130; 539-548.



- 5-CT controls (n=8)
- ▲ SB-269970 0.03 μM (n=7)
- ▼ SB-269970 0.1 μM (n=8)
- ◆ SB-269970 0.3 μM (n=8)
- ▼ SB-269970 1 μM (n=8)



Schild Plot slope = 0.91 ± 0.11
 X intercept = $pA_2 = -8.77$

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ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by Faculty of Pharmaceuticals Sciences, University Paul Sabatier, Toulouse, France.