Piboserod (SB 207266), a selective 5-HT<sub>4</sub> receptor antagonist, reduces serotonin potentiation of neurally-mediated contractile responses of human detrusor muscle

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ABSTRACT

Piboserod (SB 207266), a selective 5-HT<sub>4</sub> receptor antagonist, reduces serotonin potentiation of neurally-mediated contractile responses of human detrusor muscle.

INTRODUCTION & OBJECTIVE

- Beneficial effects of the gastrointestinal prokinetic 5-HT<sub>4</sub> agonist cisapride have been reported on voiding disorders in patients with urinary retention due to acquisitive bladder after spinal cord injury 1. Additionally, an increase in micturition frequency has been described in patients treated with cisapride for gastrointestinal motor disturbances 2,3.

- In vitro, 5-HT has been shown to enhance the contractile responses to electrical field stimulation (EFS) of isolated human detrusor strips by facilitating the neuromuscular parasympathetic cholinergic transmission 4. The 5-HT receptor mediating this potentiating effect has been pharmacologically identified as the 5-HT<sub>4</sub> receptor subtype located prejunctionally on the cholinergic terminations within the detrusor wall.

- To our knowledge, there is no available clinical data regarding the effect of a 5-HT<sub>4</sub> antagonist on bladder function. Nevertheless, considering the properties of 5-HT<sub>4</sub> agonists, a selective 5-HT<sub>4</sub> receptor blockade may have a potential role in the treatment of overactive bladder for which a decrease of cholinergic stimulation is expected to be beneficial 5.

METHODS

- Human detrusor strips preparation

Samples of human bladder were obtained from patients undergoing cystectomy for infiltrating bladder cancer (57 ± 2.5 years old). All bladder samples were collected with patient informed consent according to local regulations. Only samples from donors with no known bladder dysfunctions were used. A macroscopically normal part of the done with no tumourous tissue was selected for experiments and detrusor strips (5 x 2 mm) were prepared by removing serosal and mucosal layers.

- Characterization of the response to electrical field stimulation (EFS)

Experiments were performed in presence of methysergide (1 µM) and ondansetron (1 µM) to block 5-HT<sub>1A</sub> and 5-HT<sub>4</sub> receptors, respectively. Results. As previously described, 5-HT potentiated the contractile response to EFS in human bladder strips in a concentration-dependent manner, with a maximum of 60 ± 19.9% of the basal EFS-activated contractions. Piboserod did not modify basal contractions (before 5-HT) but induced a concentration-dependent antagonism of the 5-HT<sub>4</sub> receptor-mediated tone and no intrinsic 5-HT<sub>4</sub> receptor activity in normal human bladder.

CONCLUSION

This study confirms the enhancing effect of 5-HT on the neurally-mediated contractile response of normal human bladder strips and it shows the ability of piboserod, a 5-HT<sub>4</sub> receptor antagonist, at antagonizing this potentiation effect.

In absence of 5-HT, piboserod had no effect on EFS-evoked bladder strip contractions, suggesting a lack of 5-HT<sub>4</sub> receptor-mediated tone and no intrinsic 5-HT<sub>4</sub> receptor activity in normal human bladder.

Nevertheless, the question that remains to answer is whether the endogenous 5-HT levels and/or the ability of 5-HT to enhance cholinergic neuromuscular transmission are increased in human idiopathic overactive bladder (OAB). Whether piboserod could alter the 5-HT<sub>4</sub>/5-HT<sub>3</sub> pathway-mediated facilitation of neurotransmission in idiopathic OAB will require further investigations. This should provide a key argument for supporting the clinical exploitation of a 5-HT<sub>4</sub> receptor antagonists such as piboserod for the management of voiding disorders associated with OAB, for which a decrease of cholinergic stimulation is expected to be beneficial.