Mirabegron and succinate in the control of bladder contraction

Cammisotto P, Mossa A, Nguyen H, Velasquez Flores M, Campeau L.
Lady Davis Institute for medical research, McGill University, Jewish General Hospital

Background

Mirabegron is a beta-3 adrenoceptor agonist prescribed for the treatment of overactive bladder disease, leading to muscle relaxation and increased in bladder capacity by binding to the receptors on smooth muscle cells. Its action on urothelial cells has not been clearly established. Succinate, an intermediate of the Krebs cycle, has similar relaxing properties in vivo in rats and on bladder strips in organ bath.

The aim of our study is to determine the differential action of mirabegron on urothelial and smooth muscle cells, and if succinate could enhance mirabegron’s relaxing effects.

Materials

Urothelial and smooth muscle cells were isolated from female Sprague-Dawley rat bladder. Cells were cultured at P2-P6 passages and processed for IHC, q and RT-PCR and immunoblotting. Cyclic AMP and PGE2 were assessed by Elisa kits. Nitric oxide was measured using the Griess reaction. Organ bath was carried out on DMT equipment.

Results

β3-adrenergic receptors are expressed in urothelial cells and SMCs in culture as revealed by PCR (A) and dPCR (B). (n=4) Student t-test P<0.05. (C) IHC was used to reveal the localization of β3-adrenergic receptors in the bladder wall (D)(From left to right, negative control, urothelium, detrusor muscle, bar = 100 μm) and in vitro (From left to right, negative control, urothelial cells, SMCs, bar = 50 μm).

(A) Succinate (200 μM) or mirabegron (10 μM) with urothelial cells for 24 hours increases nitric oxide (NO) secretion and NOS expression. No synergic effect was observed.

(B) Succinate (10 μM) or mirabegron (10 μM) decreases basal secretion of prostaglandin E2 (PGE2) in urothelial cells while combination of both compounds results in high release of PGE2. No effect was seen on SMCs (n=6). One-way ANOVA *P<0.05 compared with control; **P<0.01 compared with control.

Conclusions

In urothelial cells, mirabegron and succinate both increase nitric oxide secretion, decrease PGE2 release and increases expression of survival genes. In smooth muscle cells, the effect of mirabegron is limited to increases in cyclic AMP while succinate has none. These results suggest that a combination of mirabegron and succinic acid could increase the direct relaxing effect of mirabegron on smooth muscle cells by enhancing the secretion of relaxing factors by urothelial cells.