MONASH University

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Mechanistic evidence to support the use of combination therapy to better manage the treatment of LUTS associated with BPH

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Introduction

There is ample clinical and experimental evidence to suggest that monotherapy, using phosphodiesterase (PDE) 5 inhibitors or selective α-blockers, ameliorates the lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) by reducing prostatic smooth muscle tone.

In this study, we provide mechanistic evidence that treatment strategies utilising a combination of phosphodiesterase 5 inhibitors and selective α-blockers may be more efficacious than either drug alone, in the management of LUTS associated with BPH.

Hypothesis

Our overall hypothesis is that changes in the mechanisms regulating spontaneous activity of the prostate gland, significantly contribute to the pathogenesis of BPH.

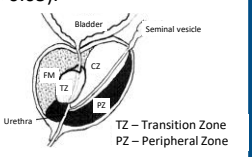
Objectives

The aim of this study was to examine the direct effect of a clinically used PDE5 inhibitor, sildenafil, alone and in combination with an existing well established treatment for BPH, the α1 antagonist tamsulosin, in a novel model of human prostatic contractility

Study design, materials and methods

Transition zone (TZ) tissue (10mm X 15mm) from the prostate gland was obtained from consenting patients undergoing radical prostatectomy. Contractile recordings were made from prostatic preparations (5mm X 10mm) using standard tension recording techniques as we have previously described. A paired Student's t-test was used to test for statistical significance ($P < 0.05$).

Figure 1. *The different zones of the human prostate gland. Figure modified from (Giles LG, 2010).*



Disclosure statement

No financial disclosures

Results 1: Sildenafil significantly reduced spontaneous contractions recorded in the TZ of the human prostate gland

Transition zone (n=8)	Basal Tension (mN)	Amplitude (N g^{-1})	Duration (s)	Frequency (min^{-1})
Control	4.60 ± 0.59	0.30 ± 0.08	10.1 ± 1.1	1.57 ± 0.21
Sildenafil (10mM) t=30 minutes	4.44± 0.55 (97 ± 1%)	0.24 ± 0.10 * (73 ± 11%)	9.7 ± 1.2 (101 ± 15%)	0.93 ± 0.23* (60 ± 14 %)

* P < 0.05; Student's paired t-test

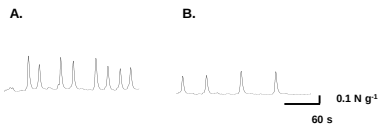


Figure 2. The effects of 10 µM sildenafil on spontaneous contractile activity in the transition zone of the human prostate gland.
4 minute traces are illustrated for ***(A)*** *control and* ***(B)*** *t=30 minutes. The amplitude and frequency of spontaneous contractions were reduced by ~ 27% and ~40% respectively, upon 10 minutes of incubation of 10 µM sildenafil.*

Results 2: Tamsulosin significantly reduced spontaneous contractions recorded in the TZ of the human prostate gland

Transition zone (n=9)	Basal Tension (mN)	Amplitude (N g^{-1})	Duration (s)	Frequency (min^{-1})
Control	4.26 ± 0.50	0.24 ± 0.04	12.5 ± 2.1	1.80 ± 0.27
Tamsulosin (0.1 nM) t=30 minutes	4.01± 0.47 ** (94 ± 1%)	0.18 ± 0.03 ** (73 ± 5%)	12.5 ± 1.8 (105 ± 7%)	1.44 ± 0.27 (80 ± 11 %)

** P < 0.01; Student's paired t-test

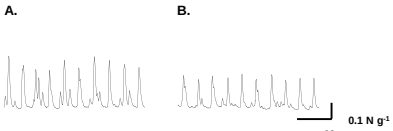


Figure 3. The effects of 0.1 nM tamsulosin on spontaneous contractile activity in the transition zone of the human prostate gland.
4 minutes traces are illustrated for ***(A)*** *control and* ***(B)*** *t=30 minutes. The amplitude of spontaneous contractions was reduced by approximately ~27% upon 30 minutes of incubation of 0.1 nM tamsulosin (Student's paired t-test, $p < 0.01$).*

Results 3: Together, sildenafil and tamsulosin significantly reduced spontaneous contractions recorded in the TZ of the human prostate gland in comparison to either drug alone

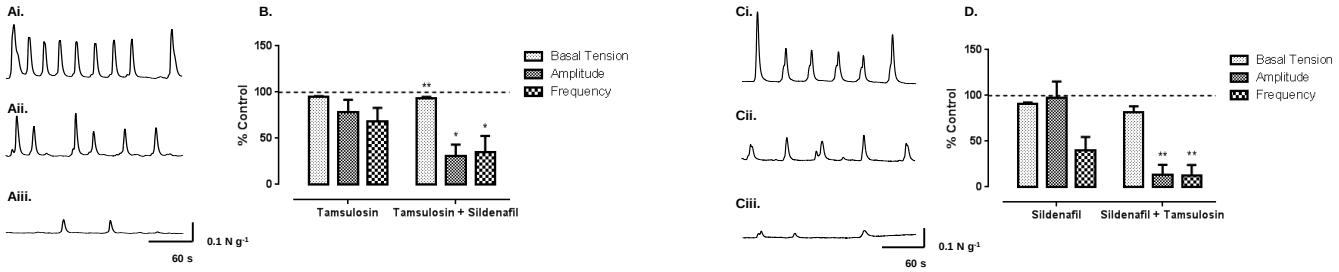


Figure 4. Combination of sildenafil (10 µM) and tamsulosin (0.1 nM) have an augmented effect on spontaneous contractions in the transition zone of human prostate tissue, compared to either drug alone.
(Ai) *Representative trace showing pre-treatment control,* ***(Aii)*** *representative trace showing pre-treatment with tamsulosin,* ***(Aiii)*** *representative trace showing treatment response of sildenafil after pre-treatment with tamsulosin.* ***(B)*** *Summary of response expressed as percentage control data for sildenafil following pre-treatment with tamsulosin.* ***(Ci)*** *representative trace showing pre-treatment control,* ***(Cii)*** *representative trace showing pre-treatment with sildenafil, and* ***(Ciii)*** *representative trace showing treatment response of tamsulosin after pre-treatment with sildenafil.* ***(D)*** *Summary of response expressed as percentage of control data for tamsulosin following pre-treatment with sildenafil (Student's paired t-test, n≥4; * indicates P < 0.05, ** indicates P < 0.01).*

Conclusion

The current study supports the notion that sildenafil and tamsulosin have a direct inhibitory effect on human prostatic smooth muscle tone, with the combination of the two drugs having an enhanced effect on human prostatic smooth muscle tone, in comparison to either drug alone. Given that LUTS / BPH and erectile dysfunction share common pathophysiology, treatment strategies using combination therapies of PDE5 inhibitors and alpha 1 antagonists may be more efficacious than either drug alone, in the management of BPH in men with or without erectile dysfunction. Further studies are needed to assess long term safety and efficacy.

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