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# **Is relaxation of human detrusor by sildenafil relying on PDE5 inhibition ?**

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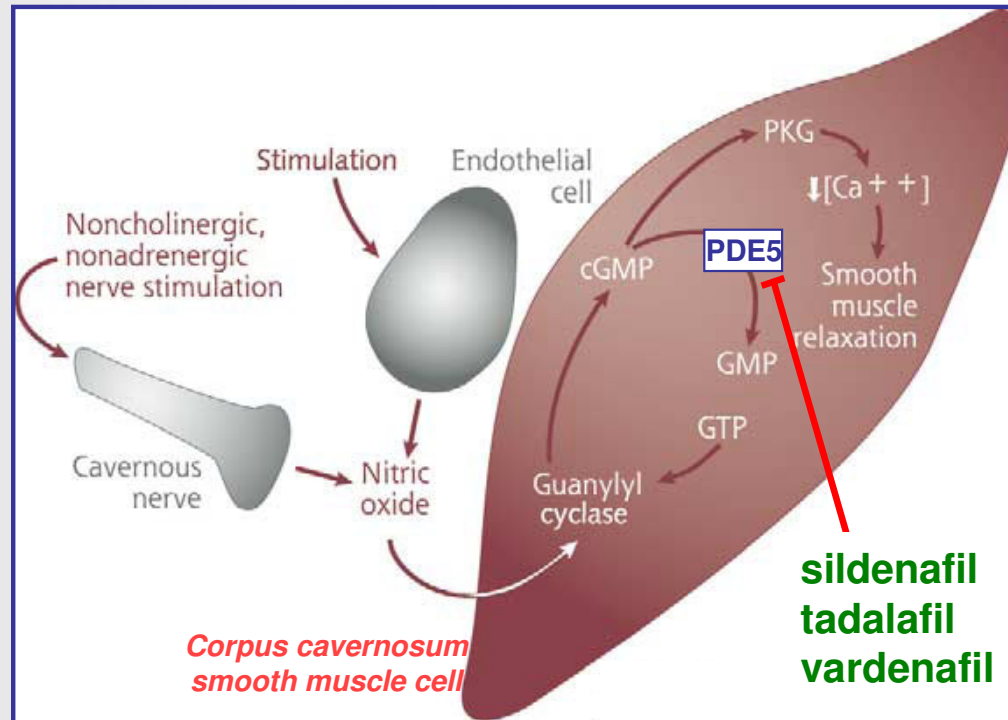
***EAU Congress, Stockholm,***

***March 19, 2009***

**PELVI PHARM**

# Introduction

- PDE5 inhibitors: first-line therapy in erectile dysfunction (ED).

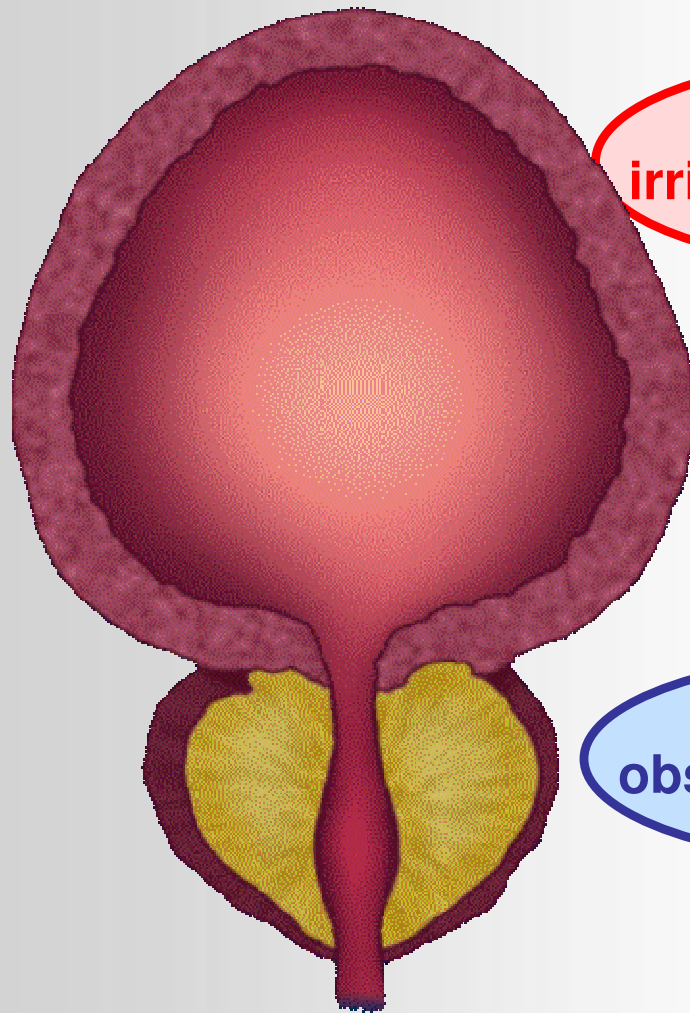


- ED is often associated with lower urinary tract symptoms (LUTS), independently of age and cardiovascular **comorbidities**

# PDE5 inhibitors for LUTS/BPH :

## Clinical trials

### Patients with LUTS associated with BPH



+++  
irritative symptoms

+++  
obstructive symptoms

- Sildenafil
- Tadalafil
- Vardenafil

### Randomized placebo-controlled trials

*McVary KT, et al J Urol*  
2007;177:1071-1077

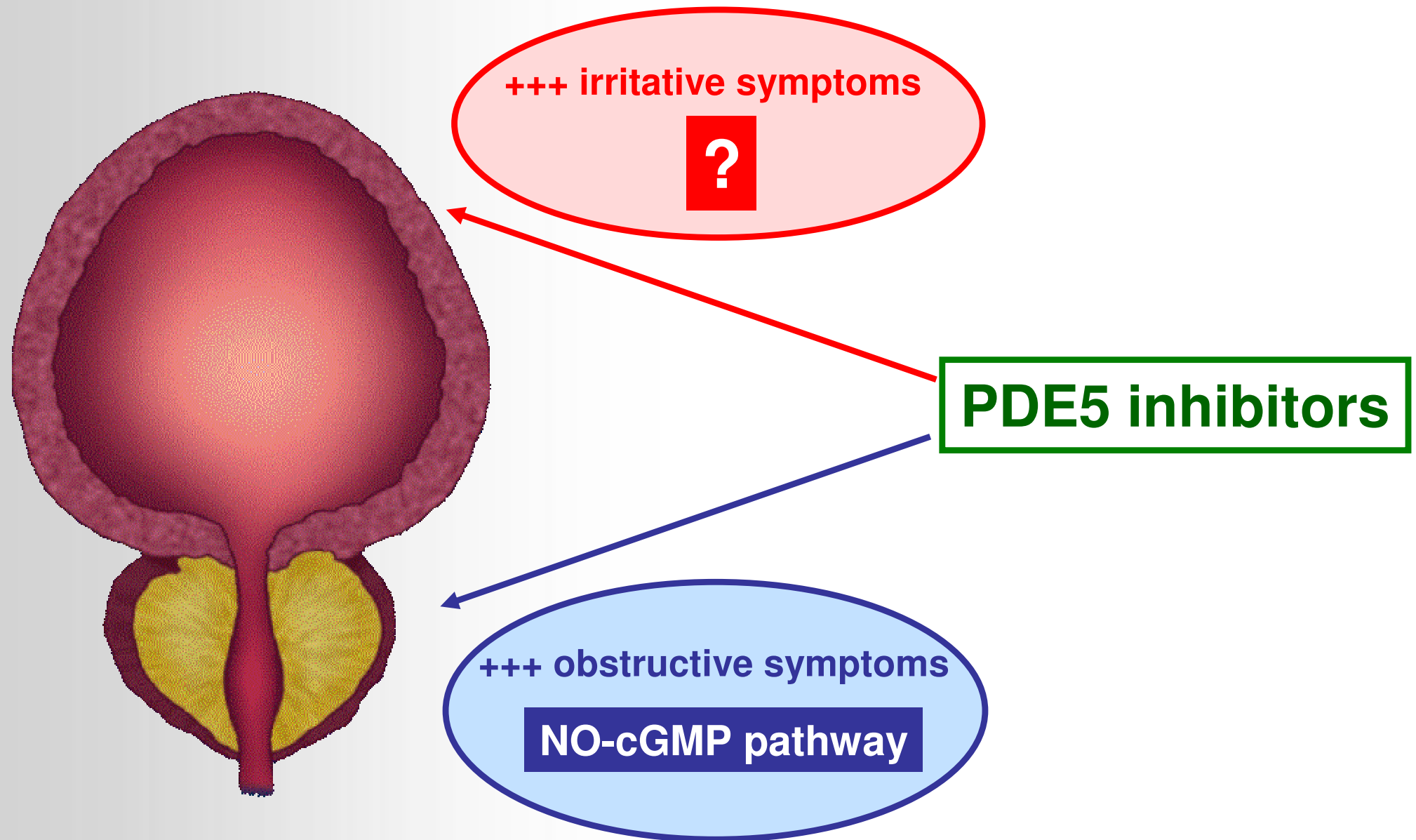
*McVary KT, et al, J Urol*  
2007;177:1401-1407

*Roehrborn et al., J Urol*  
2008; Oct;180(4):1228-34 \*

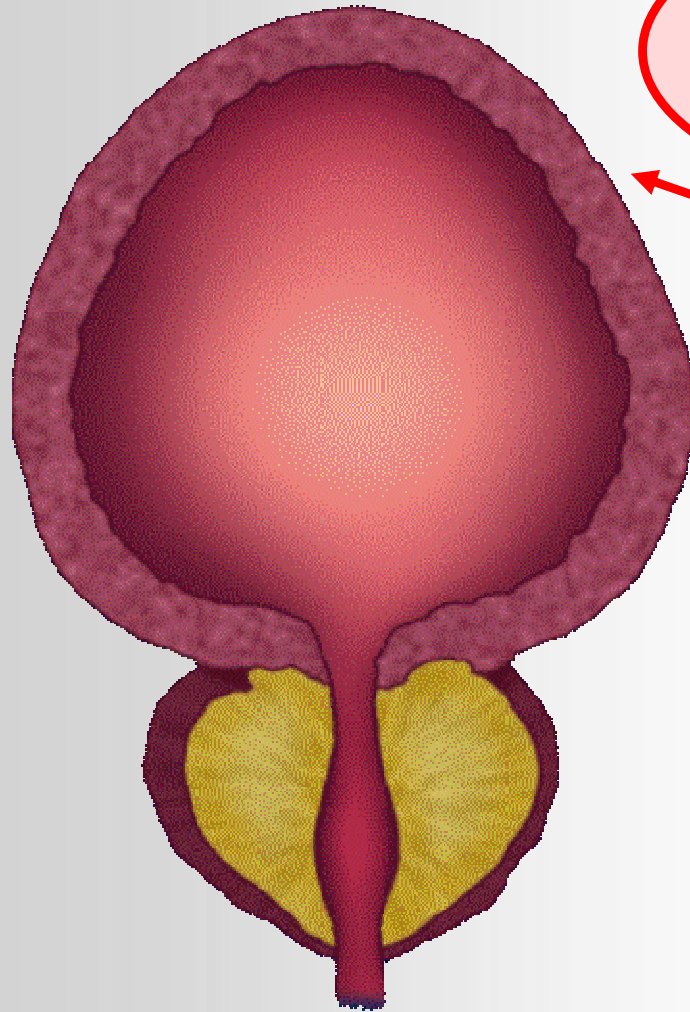
*Stief CG, et al Eur Urol*  
2008;53:1236-1244.

\*double-blinded

# Mechanism of action ?



# Objectives



+++ irritative symptoms

?

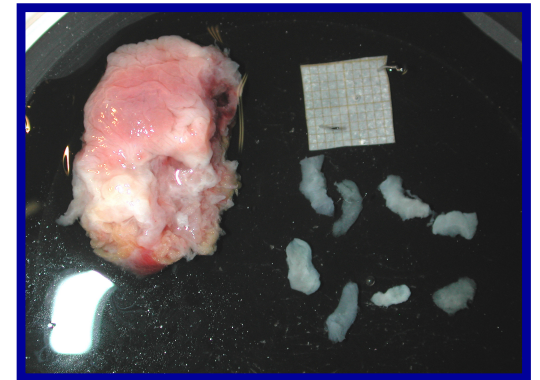
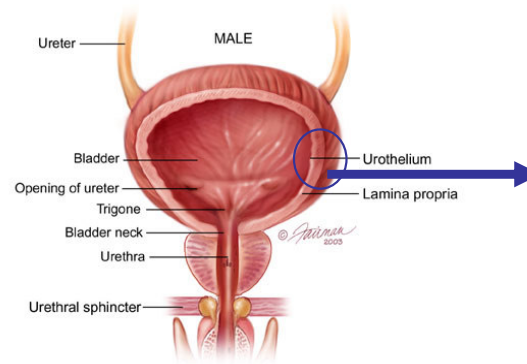
**PDE5 inhibitors**

- Assess the ability of sildenafil to relax human detrusor smooth muscle
- Investigate the signaling pathways that could be involved in sildenafil-mediated relaxation

# Experimental design

## ➤ Human bladder samples

- Bladder samples were obtained from **20 patients** ( $65 \pm 2.1$  years) undergoing cystoprostatectomy for infiltrating bladder cancer with no history of bladder dysfunction according to their medical chart.

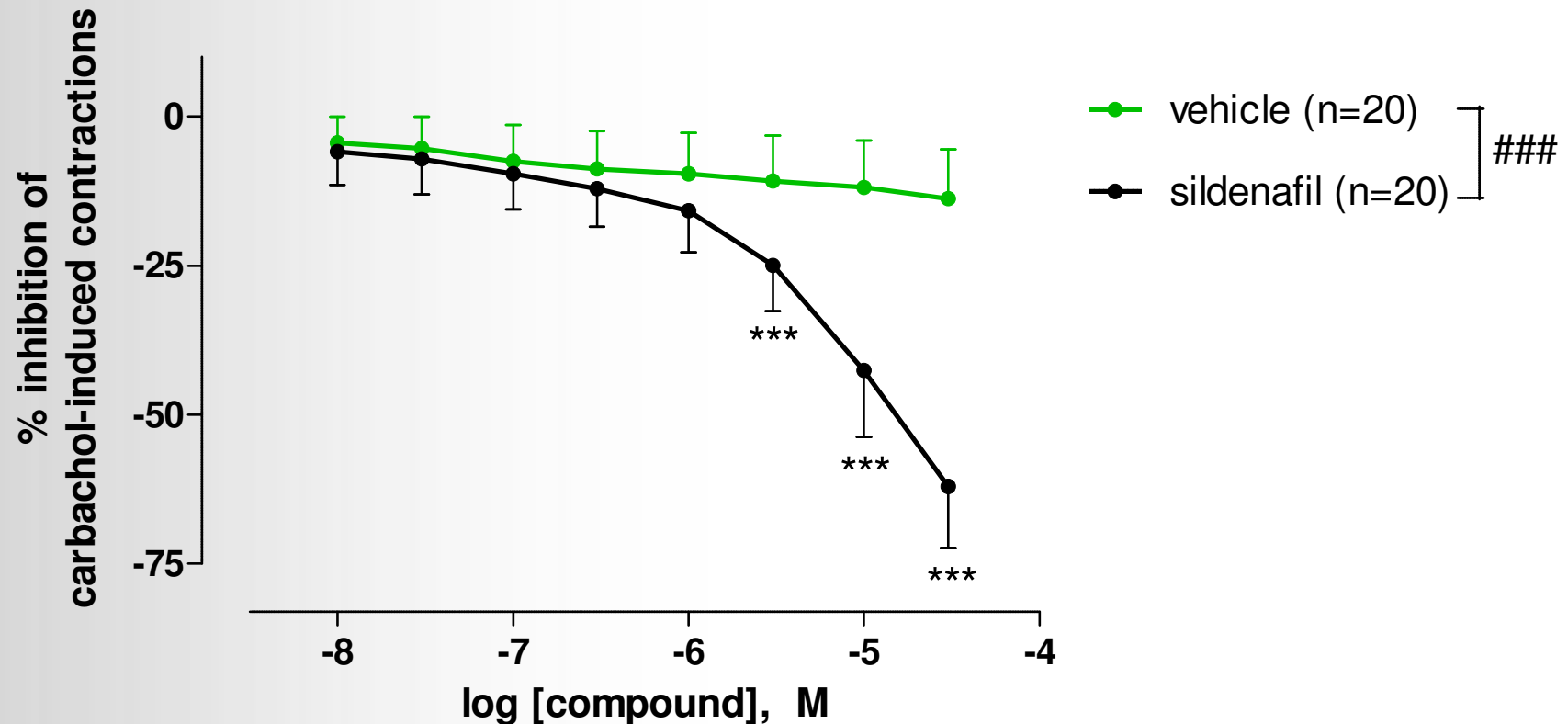


## ➤ Evaluation of the smooth muscle contractile reactivity with isolated organ baths

- Strips are excised from the tissue samples and connected to force transducers for isometric tension recording
- Organ baths are filled with Krebs buffer maintained at  $37^{\circ}\text{C}$  and bubbled with 95% $\text{O}_2$  and 5% $\text{CO}_2$ , pH 7.4



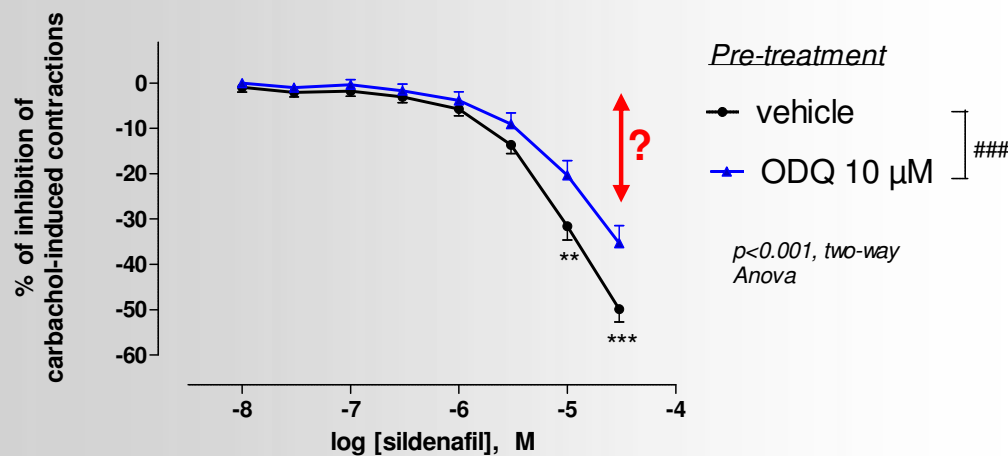
# Effect of sildenafil on carbachol-precontracted human detrusor strips



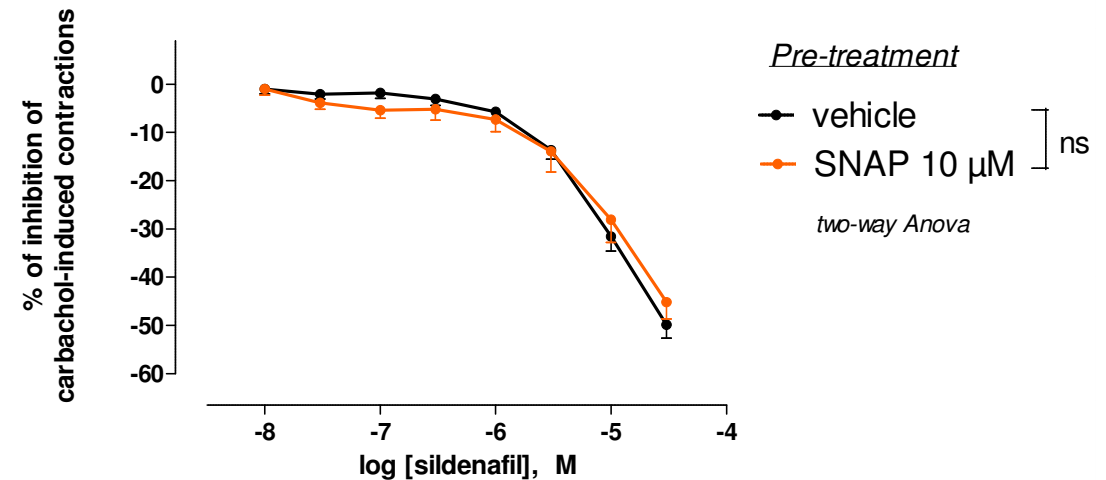
***By which mechanism of action does sildenafil relax human bladder tissue ?***

# NO/cGMP-dependent mechanism of action?

## Effect of guanylate cyclase inhibition



## Effect of a NO donor

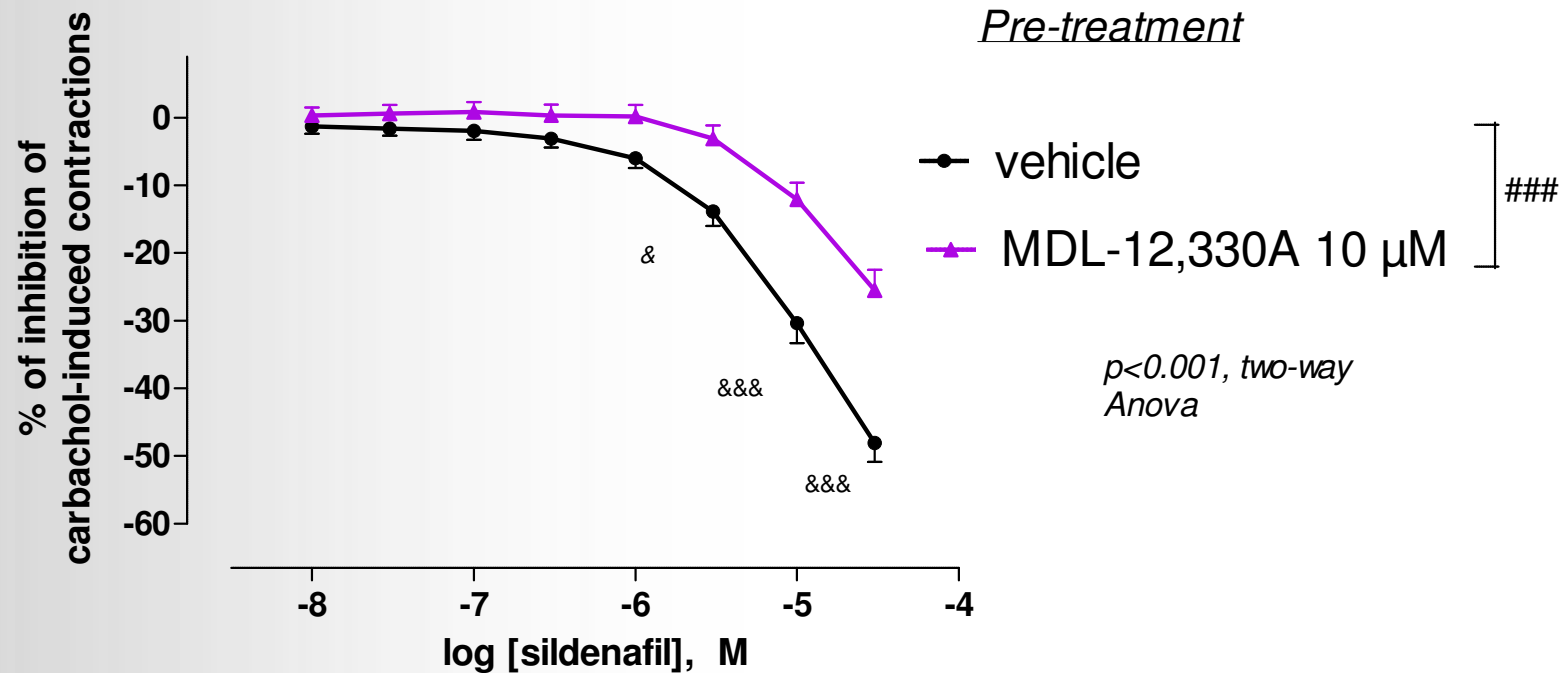


➤ Relaxation of carbachol-precontracted human bladder by sildenafil involves a cGMP-independent mechanism pathway;  
Indeed, a NO donor does not enhance sildenafil effect



# cAMP-dependent mechanism of action?

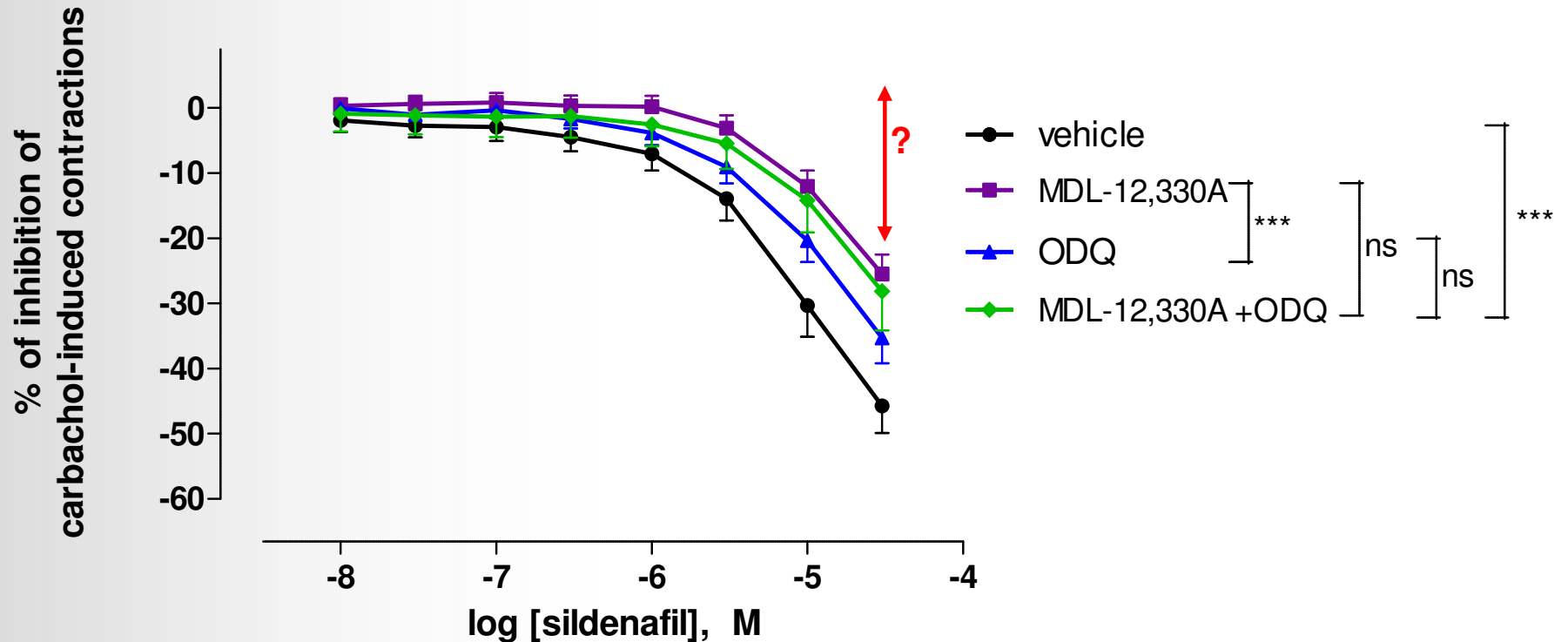
## Effect of adenylate cyclase inhibition



➤ **Sildenafil inhibits carbachol-induced human bladder contractions via a cAMP-dependent mechanism pathway**

# Other mechanisms of action ?

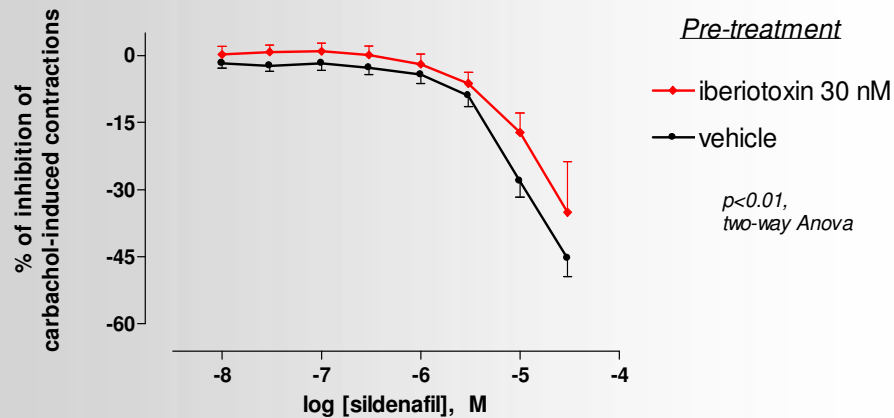
## Effect of guanylate and adenylate cyclases inhibition



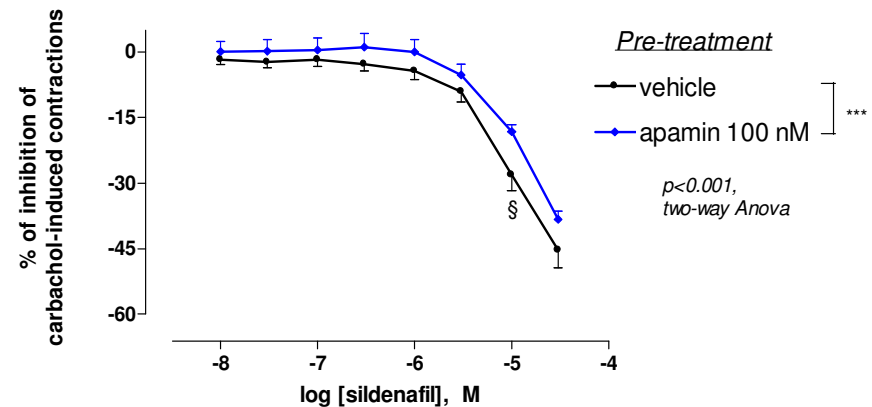
➤ Sildenafil also exerts its inhibitory effect by an other pathway, independent of cGMP or cAMP signaling pathways, since some relaxing activity remains in presence of both MDL 123,330A and ODQ

# K<sup>+</sup> channel-dependent mechanism of action ?

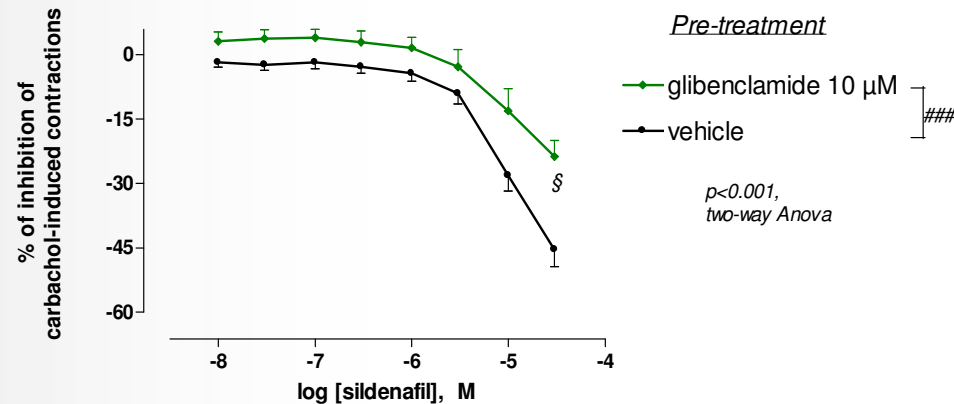
## Effect of BK<sub>Ca</sub> channels blocking



## Effect of SK<sub>Ca</sub> channels blocking



## Effect of K<sub>ATP</sub> channels blocking



**K<sub>ATP</sub>, BK<sub>Ca</sub>, and SK<sub>Ca</sub> channels are involved in the relaxation elicited by sildenafil on human detrusor tissue**

# Conclusions

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- The relaxant effect of sildenafil on carbachol-induced human detrusor contraction involves cAMP-dependent signaling pathway and K<sup>+</sup> channels dependent mechanism of action
- The contribution of the NO-cGMP signaling pathway in sildenafil-induced relaxation appears to be minor
- Sildenafil in part improves urinary symptoms in men with LUTS associated with BPH via direct relaxation of the detrusor