Ozarelix, an LHRH Antagonist, exerts a direct relaxing effect on Human Prostate in vitro

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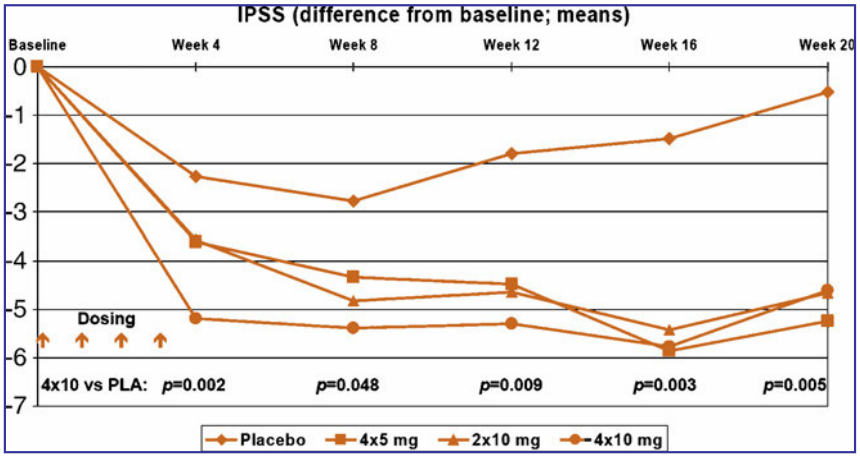
Introduction

- Clinical results demonstrate the benefit of LHRH antagonists (degarelix, tevarelix, cetrorelix and ozarelix) for the treatment of symptomatic BPH *(Debruyne et al., Eur Urol 2008)* :

✓ Significant improvement of IPSS
✓ Increase in uroflow
✓ Improvement of QOL
✓ Slight reduction in prostate volume



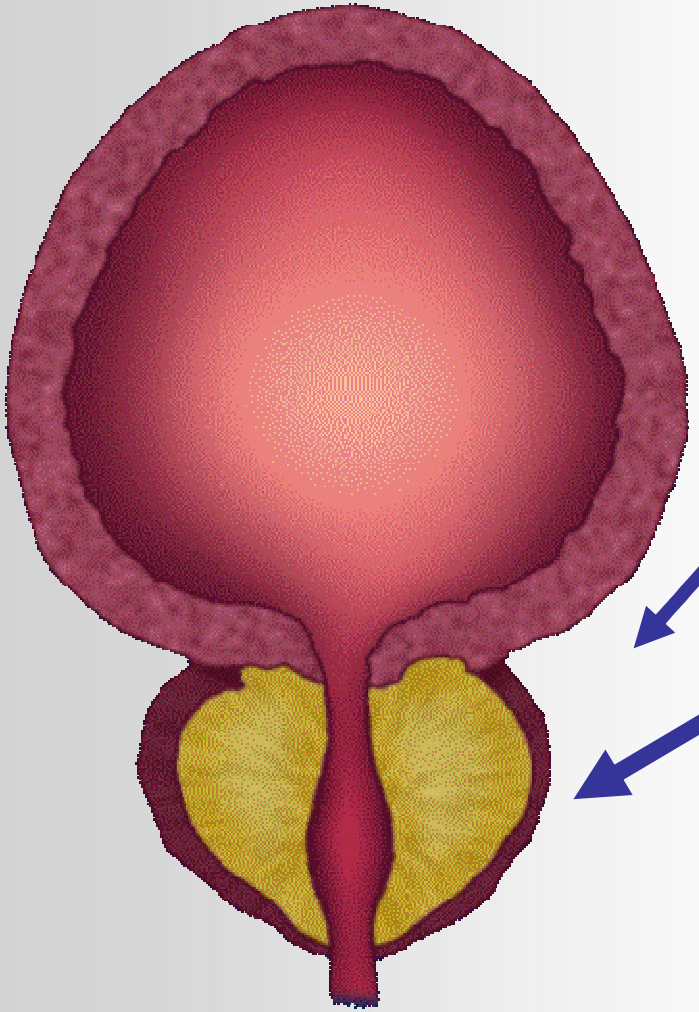
Changes in IPSS in response to Cetrorelix

- Reduction in testosterone levels transient and incomplete

- LHRH receptors are expressed in human prostate tissue

(Halmos et al, 2000; Bono et al, 2002; Engel et al, AUA 2008)

Elucidating the mechanism of action responsible for ozarelix-mediated improvement in BPH/LUTS



Improvement in voiding symptoms

Pituitary gland

Ozarelix

?

?

Reduction of prostate volume compared to baseline

- **Dynamic components of obstructive symptoms**
- **Static components of obstructive symptoms**

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Experimental design

➢ Human prostate samples

- Prostate samples were obtained from **12 patients** *(65±3 years)* undergoing cystoprostatectomy for infiltrating bladder cancer

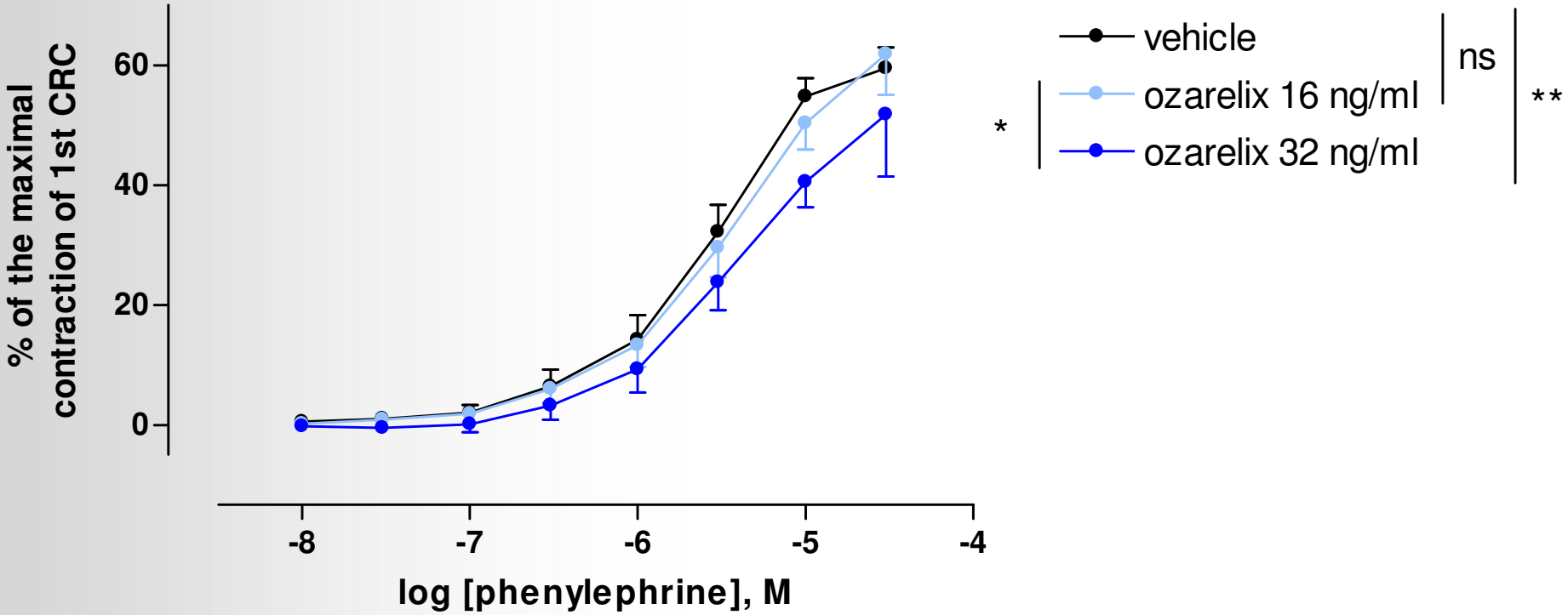
➢ Evaluation of the smooth muscle contractile reactivity with isolated organ baths

- 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°C and bubbled with 95%O2 and 5%CO2, pH 7.4

➢ Concentration-response curves to phenylephrine were constructed. Then, after a 20-minute incubation period with either ozarelix (at two different clinically meaningful concentrations) or vehicle, concentration-response curves to phenylephrine were repeated.

Effect of ozarelix on phenylephrine-induced contractions on human prostatic strips

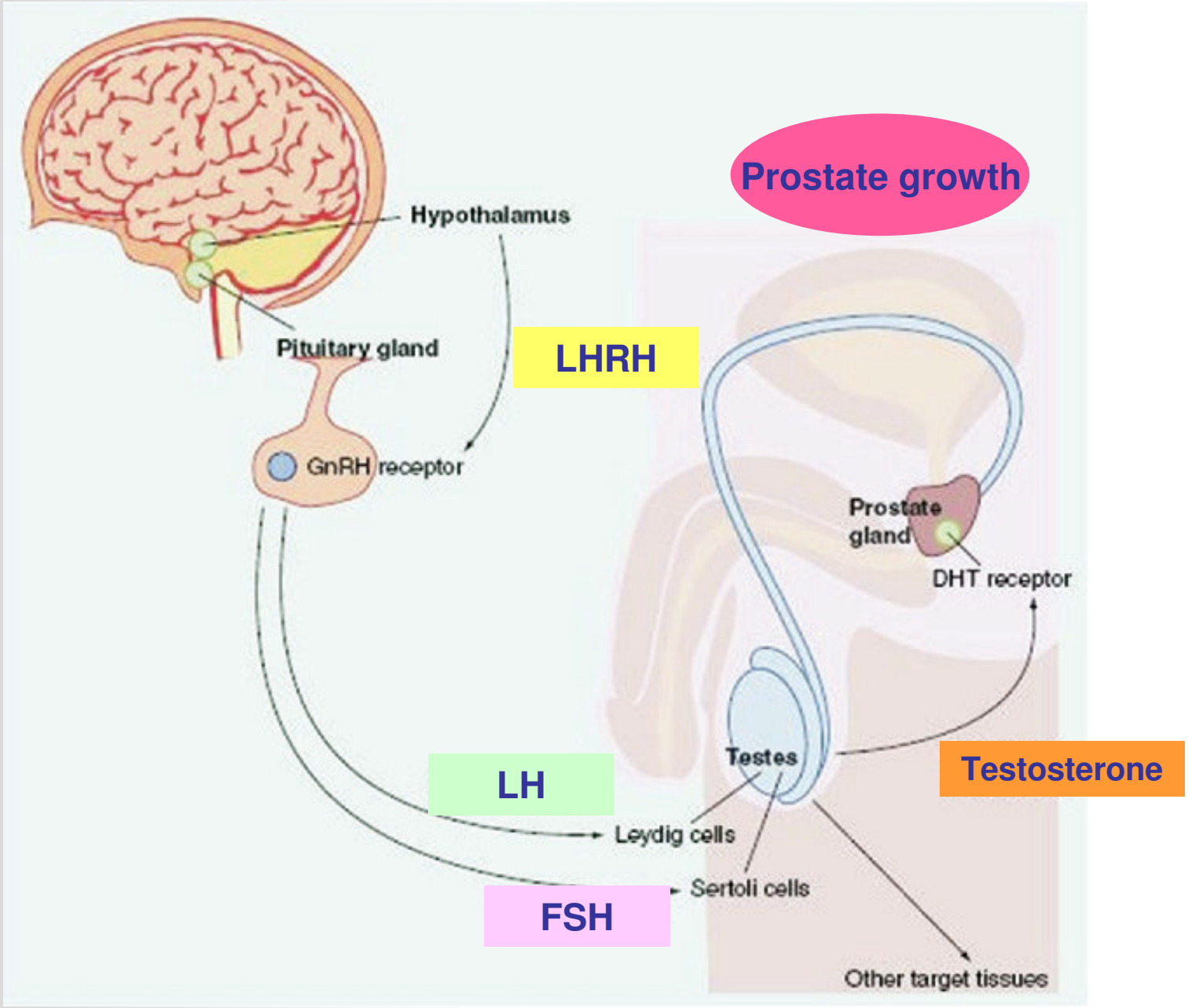


	pD2 [ns]	*Emax* [ns] *(%)*	*Maximal contraction during first CRC to PHE* [ns] *(mg)*	*N*
ozarelix's vehicle	5.64 ± 0.13	57.8 ± 3.2	887 ± 121	9
ozarelix 16 ng/ml	5.49 ± 0.11	63.6 ± 6.1	641± 137	7
ozarelix 32 ng/ml	5.56 ± 0.17	54.8 ± 9.2	591 ± 124	8

Conclusions

- Ozarelix at 32 ng/ml significantly inhibited contractions induced by PHE on human prostatic strips.
- This study provides the first evidence for a direct relaxant effect of an LH-RH antagonist on human prostate.
- This direct relaxant effect of ozarelix on pre-contracted human prostate strips may explain in part the reported rapid relief in symptoms when administered to men with LUTS/BPH.
- This study supports the development of ozarelix in the treatment of BPH

Control of testosterone-induced prostate growth by LHRH



Adapted from Poppel and Nilson, 2008, Urology 71 (6)