Oxytocin in prostate pathology

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Is there a sinister side to the “hormone of love”?

Oxytocin (the “hormone of love”) as a pharmacological agent

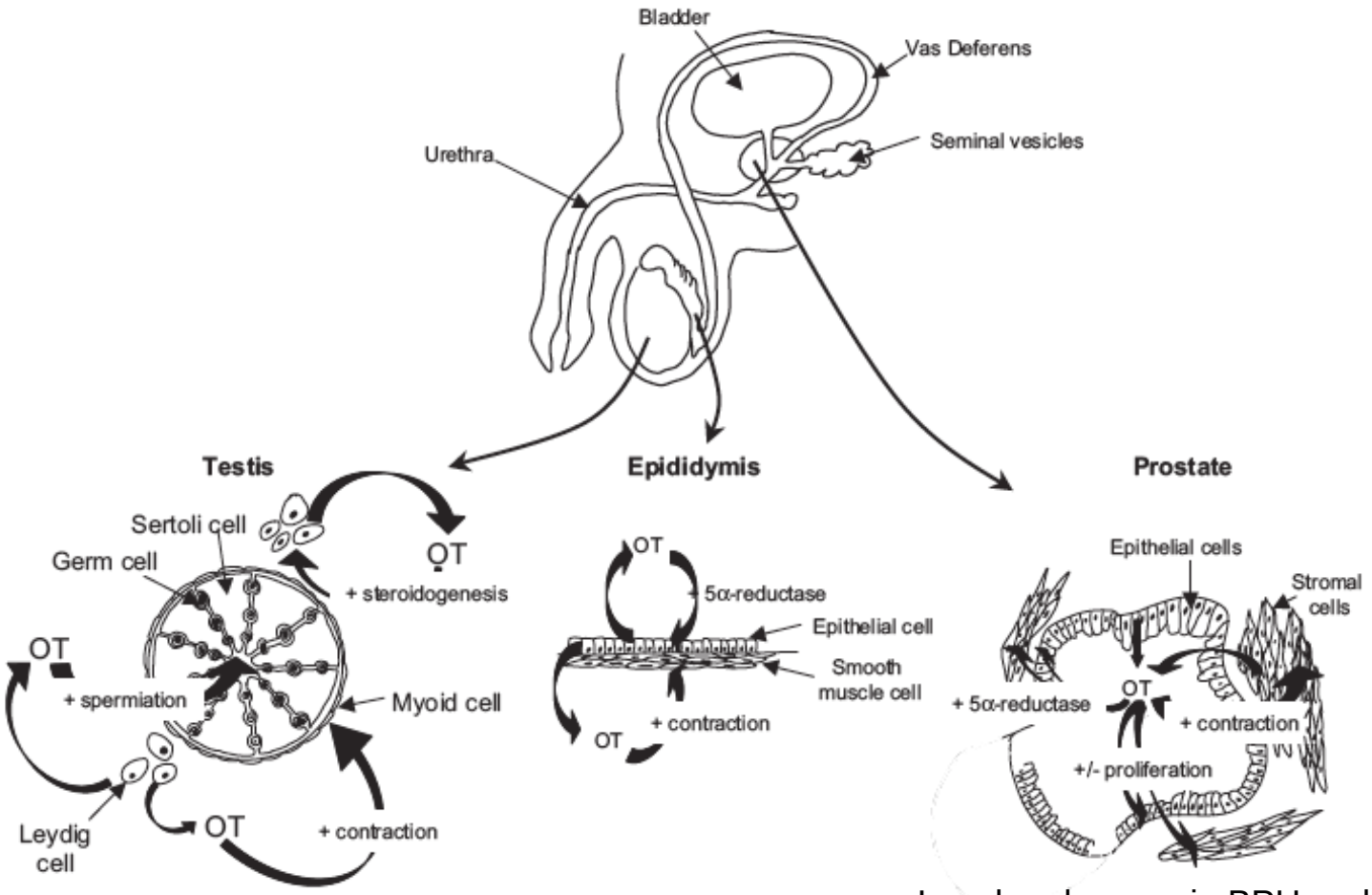
- Classical roles in parturition and milk letdown in the suckling response.
- OXT important social hormone:

  e.g. in pair bonding, trust & maternal behavior.

- Autism spectrum disorder; Schizophrenia.
- Pain management.
- Hypophagia, insulin/glucose homeostasis and weight loss.

Reviewed in Tom NC & Assinder SJ (2010). Oxytocin: Recent developments. *Biomolecular Concepts* 1: 367-380.

Peripheral oxytocinergic systems present in the male reproductive system.

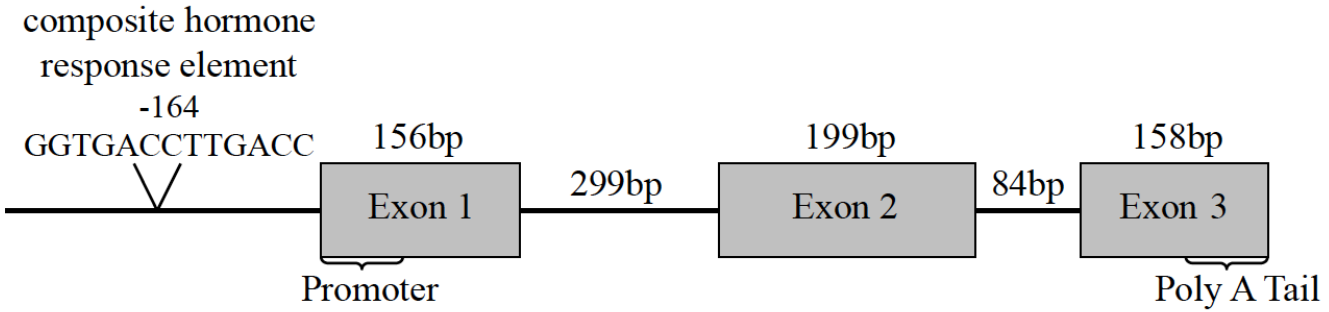


Local androgens in BPH and CaP

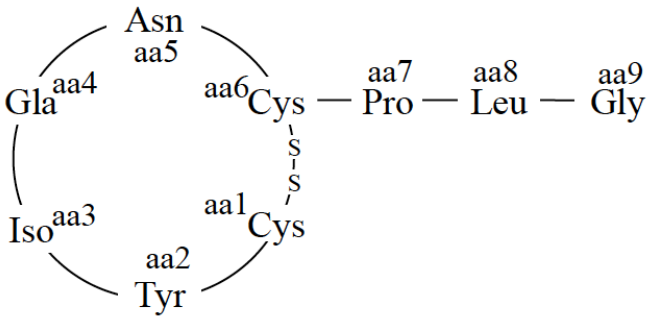
From: Thackare *et al.*, 2006 Human Repro Update 12: 437-448

Oxytocin is synthesised in the prostate.

a) Oxytocin gene structure



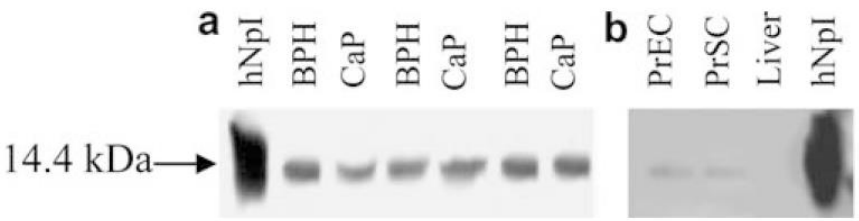
b) Oxytocin primary protein structure



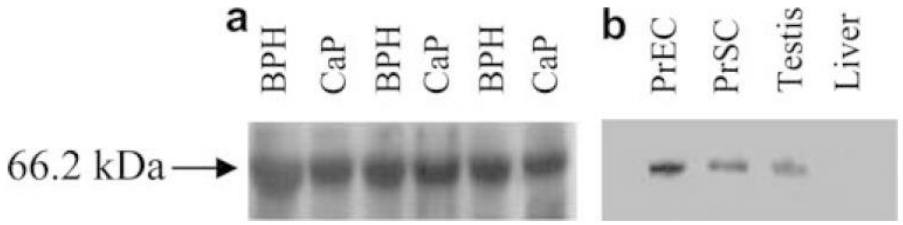
From: Assinder and Tom 2010 Int J Biochem Cell Biol 42: 202-205.

A complete oxytocinergic system is present in the prostate.

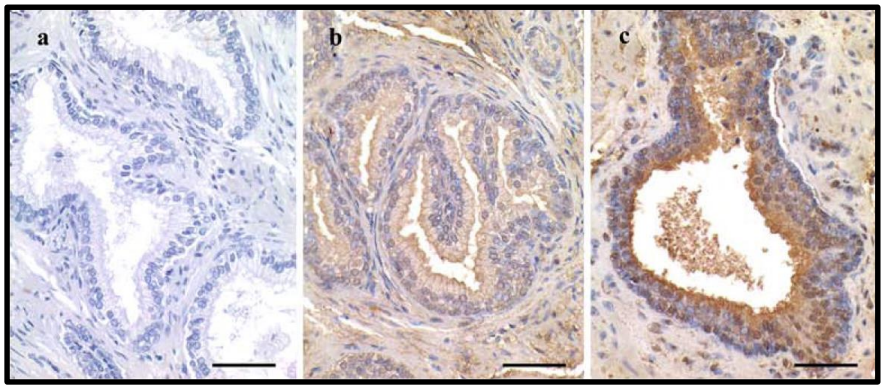
OXT



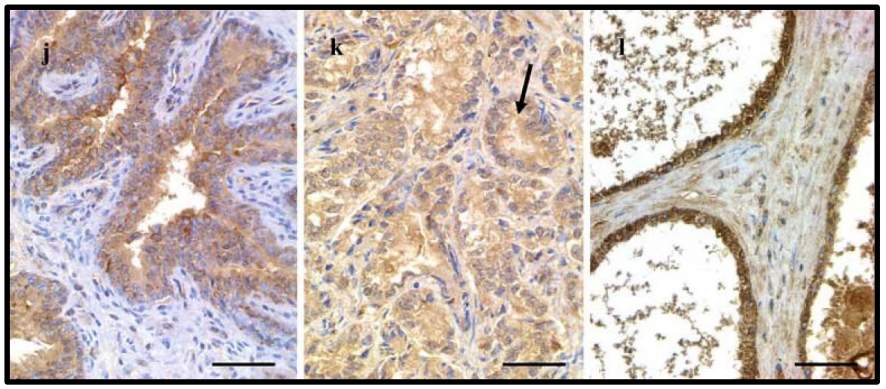
OXTR



BPH PIN

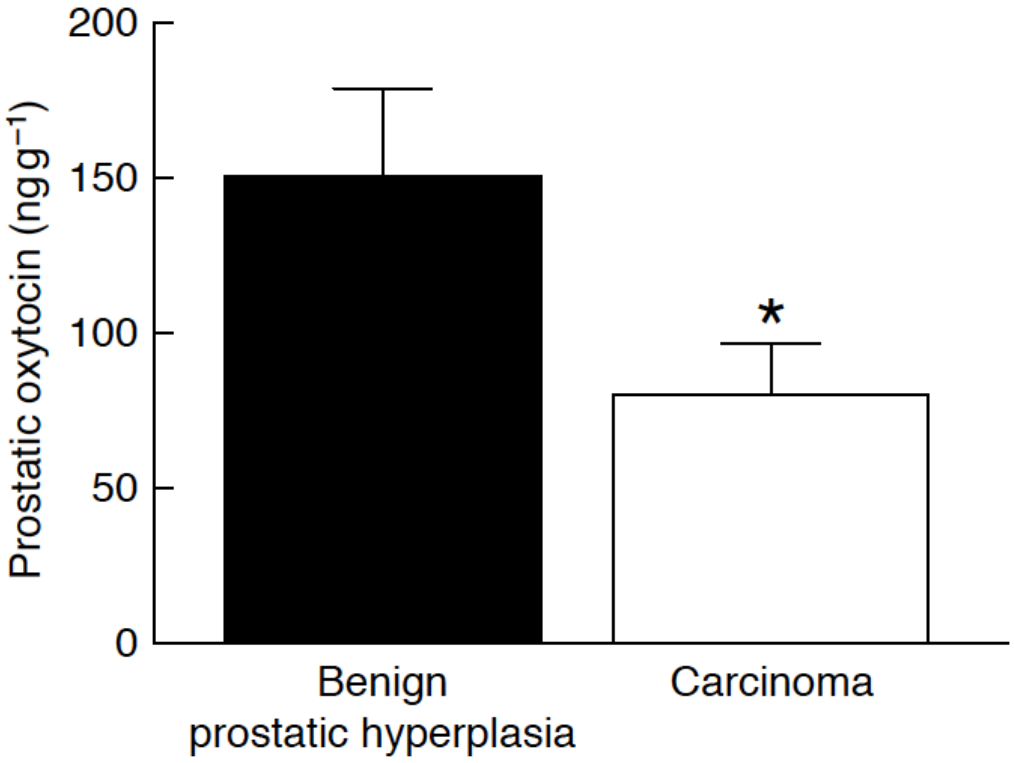


BPH IC Normal



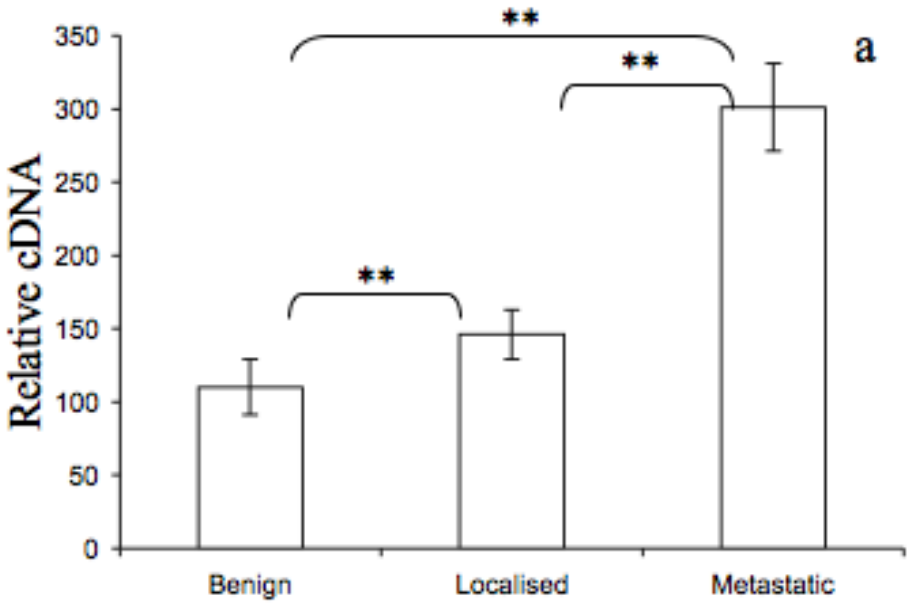
From: Whittington et al. (2004) Cell Tissue Res 318: 375-382

Oxytocin concentrations are highest in benign prostatic hyperplasia.



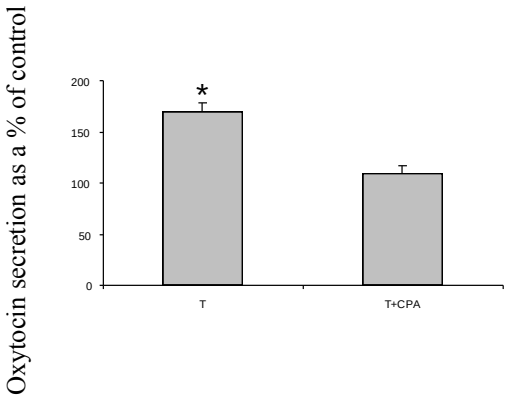
From: Nicholson 1996 Rev Repro 1: 69-72

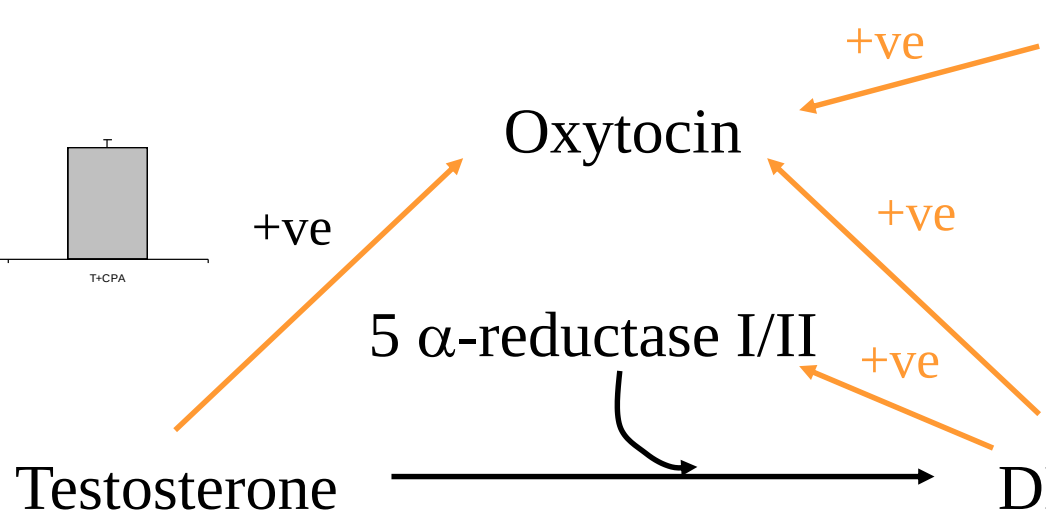
Oxytocin receptor is highest in prostate cancers.

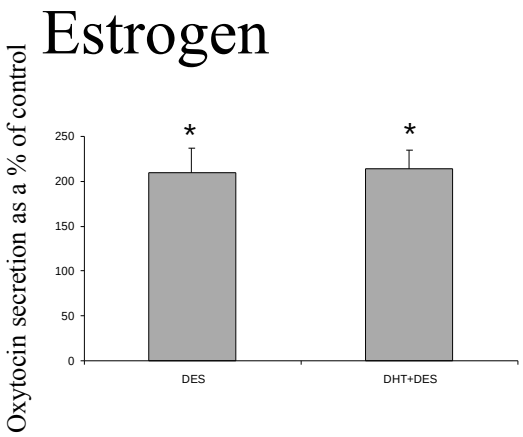


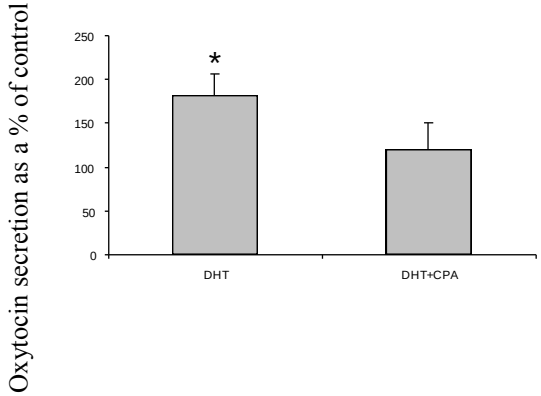
Assinder (2010) Oxytocin in the Pathophysiology of Prostate Cancer. In: Handbook of Oxytocin Research: Synthesis, Storage and Release, Actions and Drug Forms. (Eds Jastrow H, Feuerbach D). Nova Science, NY. Chapter 7 pp. 157-170.

Sex steroids increases OXT in BPH tissue



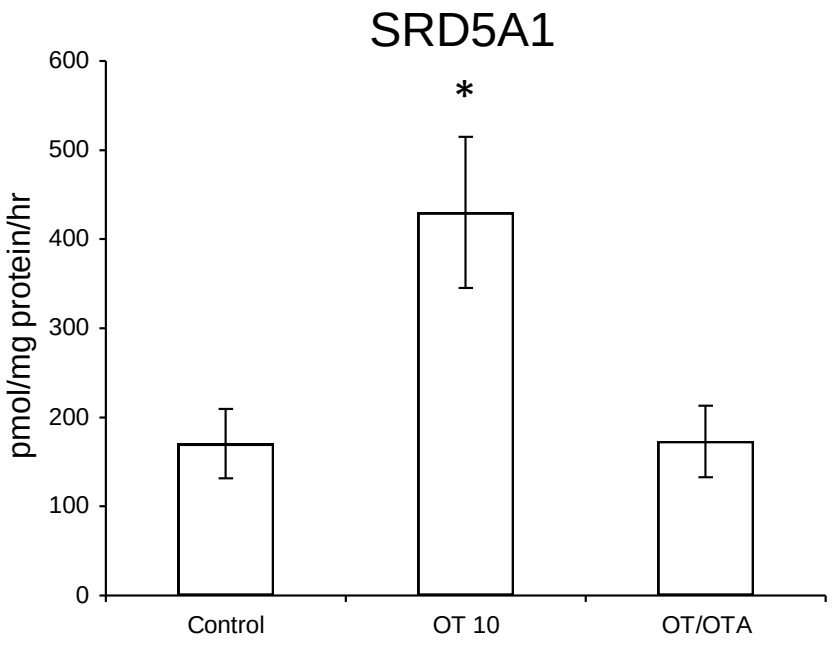


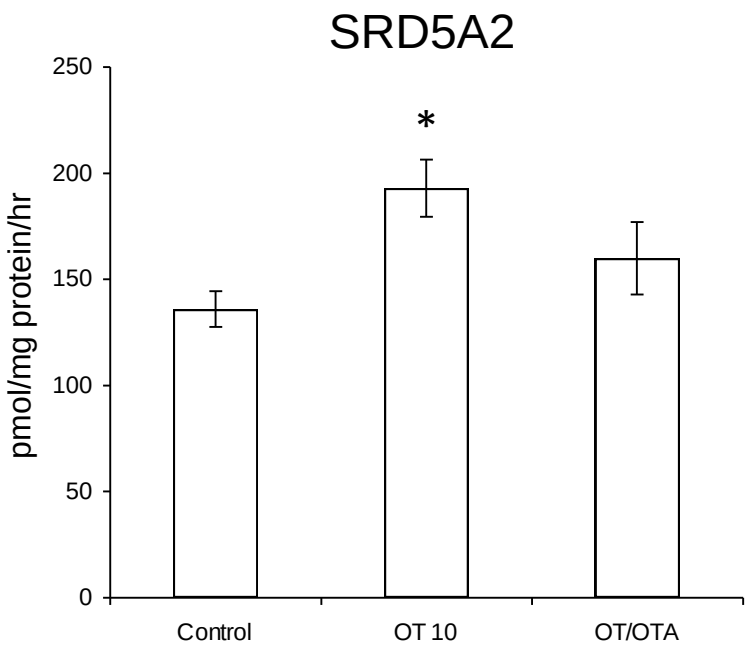




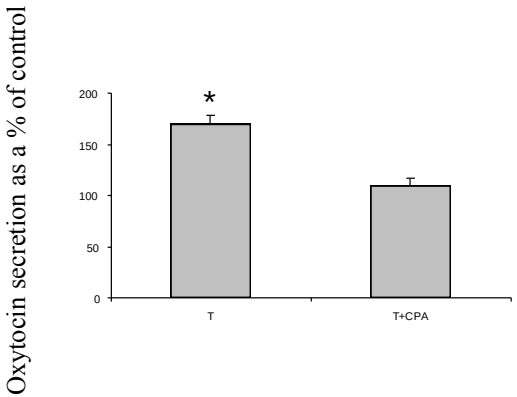
Assinder & Nicholson (2004) *Int J Andrology*, **27**, 12-18

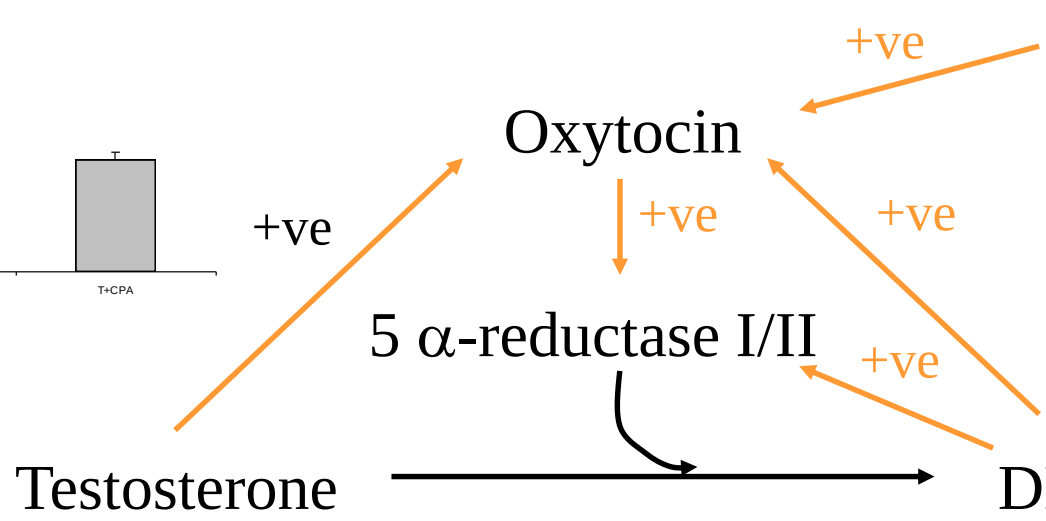
OXT increases SRD5A1 and 2 in normal prostate epithelial cells

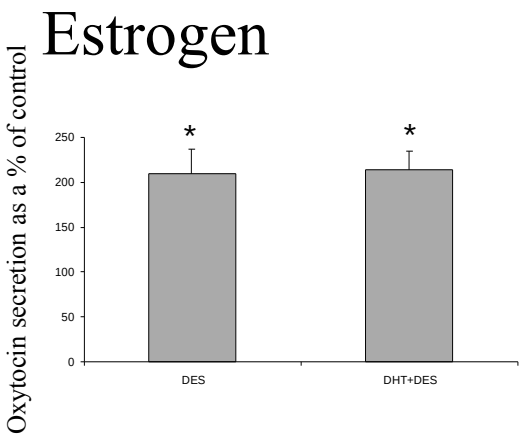


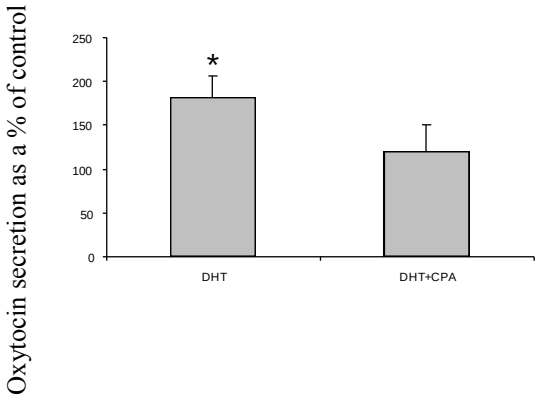


Sex steroids increases OXT in BPH tissue









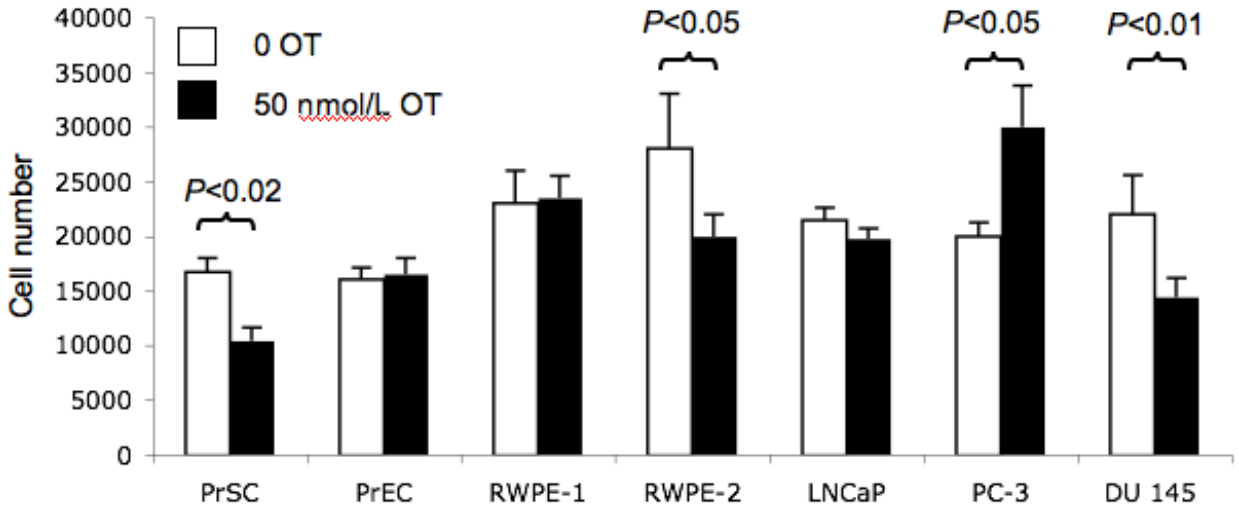
Androgen Receptor

Proliferation?

Assinder & Nicholson (2004) *Int J Andrology*, **27**, 12-18

Oxytocin has differential effects on cancer cell proliferation

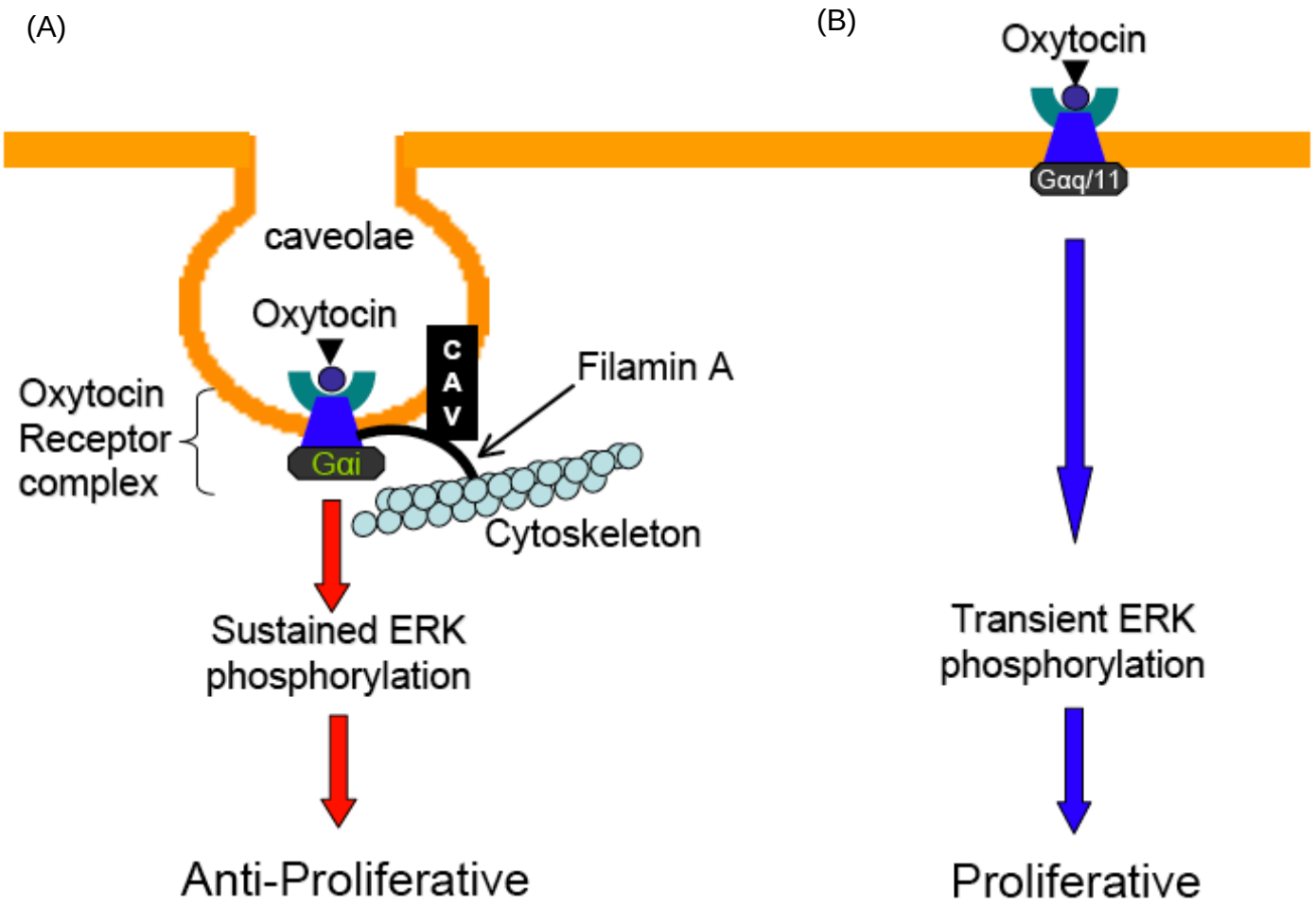
- Oxytocin increases proliferation of sc-lung carcinoma and choriocarcinoma, but inhibits ovarian and endometrial cancer cells.
- Breast cancer cells exhibit positive and negative responses.
- Oxytocin either inhibits, stimulates or has no effect on prostate cancer cell proliferation.



Assinder (2010) Oxytocin in the Pathophysiology of Prostate Cancer. In: Handbook of Oxytocin Research: Synthesis, Storage and Release, Actions and Drug Forms. (Eds Jastrow H, Feuerbach D). Nova Science, NY. Chapter 7 pp. 157-170.

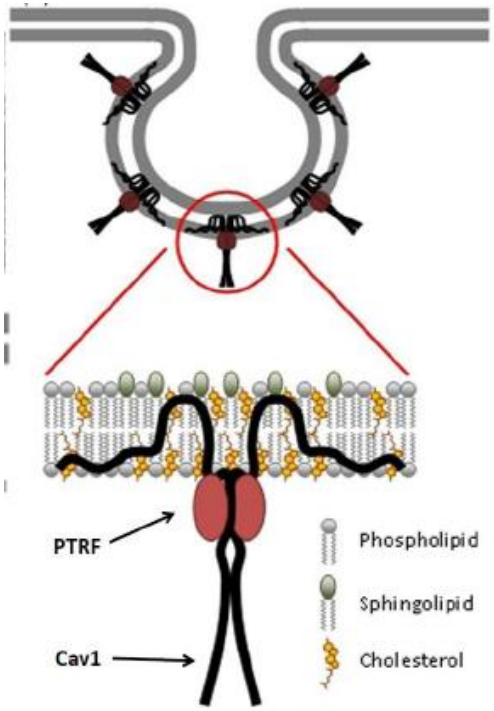
Two hypotheses for differential effects:

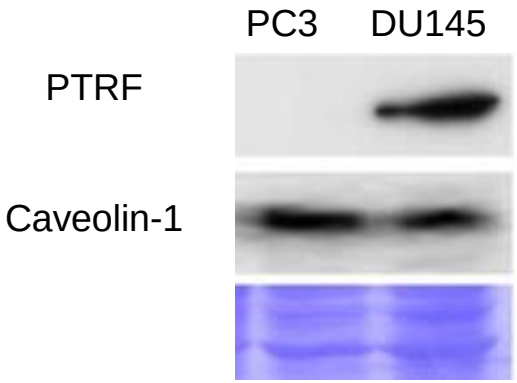
1. Different receptor localisation
2. Different Gα subunits coupled to the OXTR



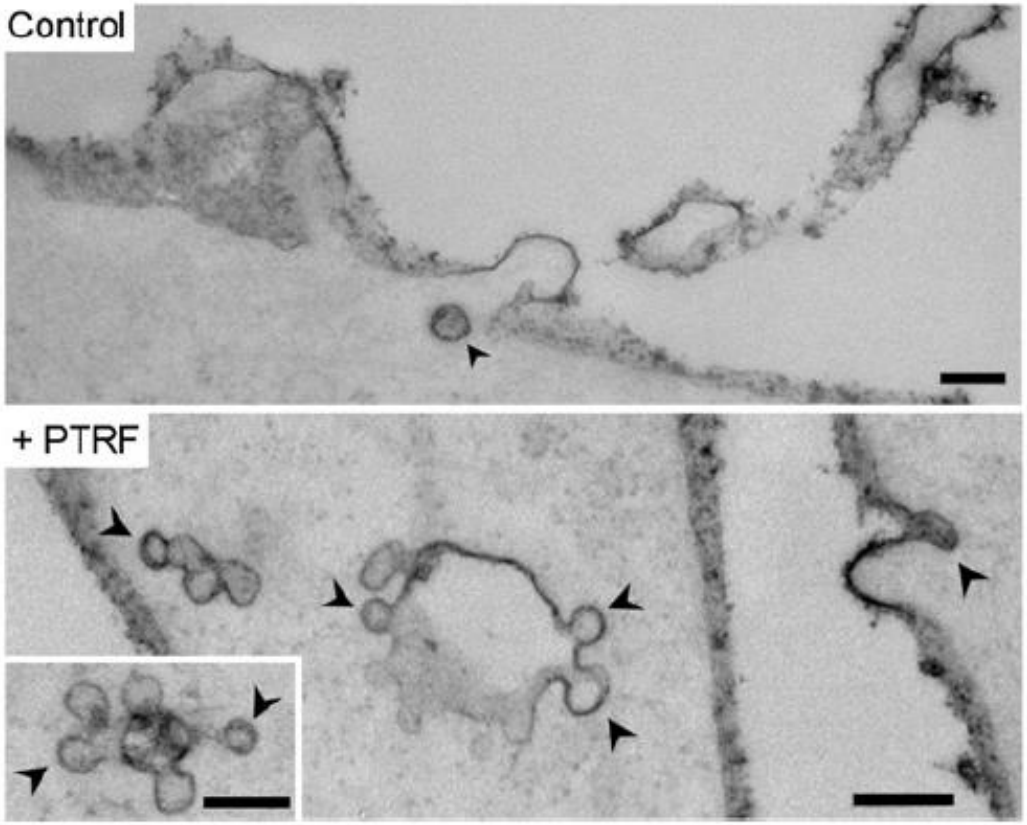
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PC-3 cells do not form caveolae, but DU 145 do



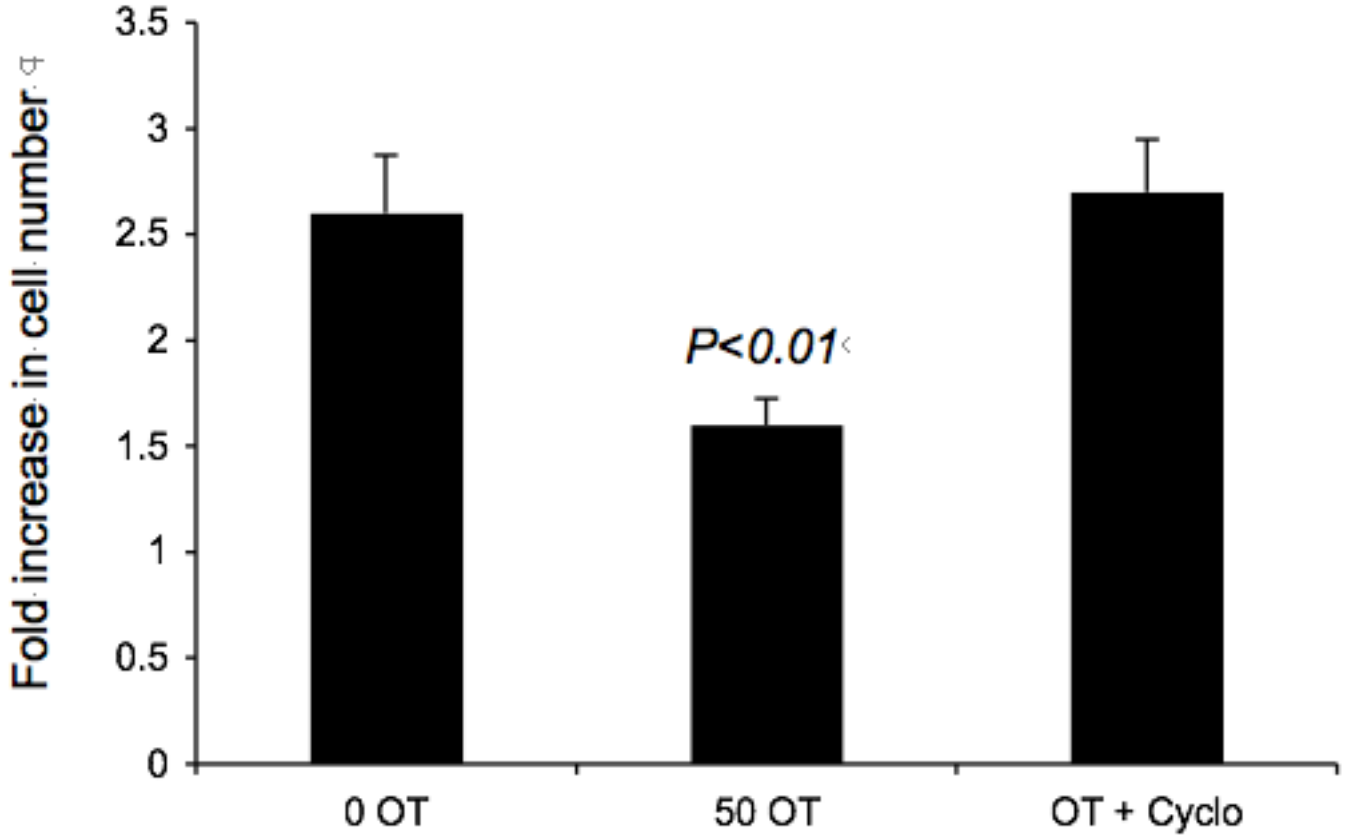


Forced expression of PTRF in PC3 results in caveolae formation (Hill *et al*. (2008) Cell; **132**, 113-124.)

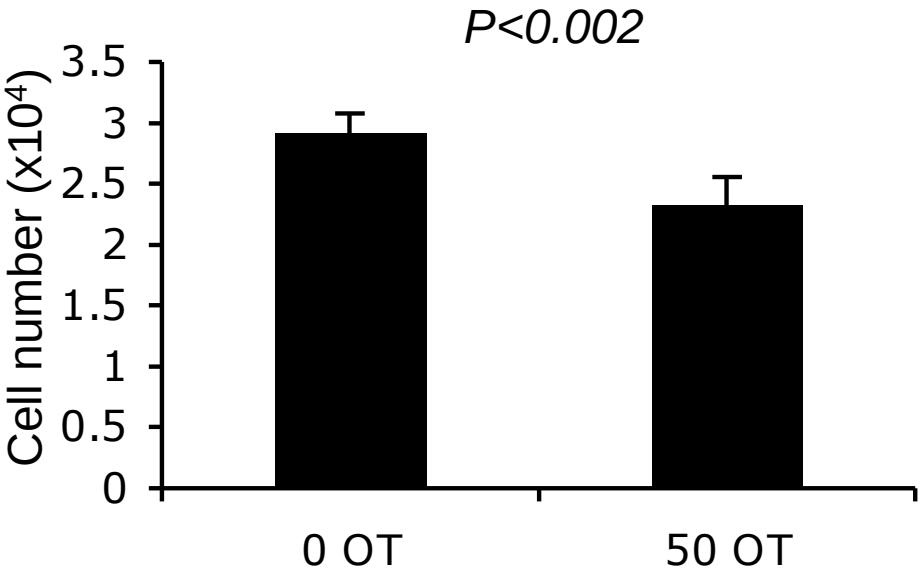


Taken from Hill *et al.* (2008) Cell; **132**, 113-124.

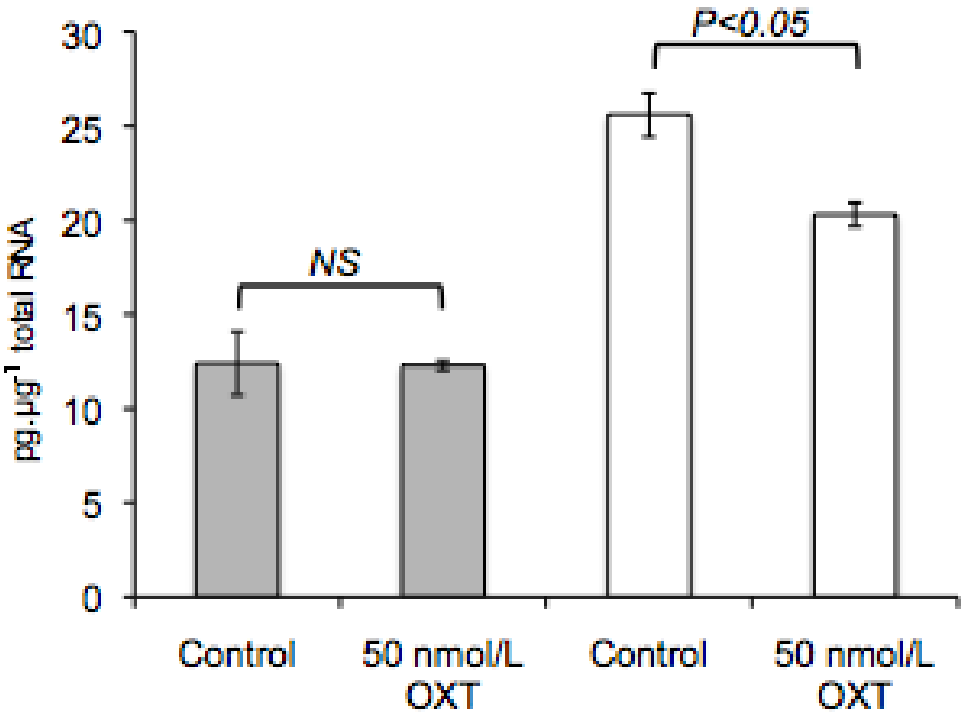
Dispersal of caveolae attenuates inhibitory effect of OXT in DU 145



Induced formation of caveolae through forced expression of PTRF results in inhibition of cell proliferation in PC-3



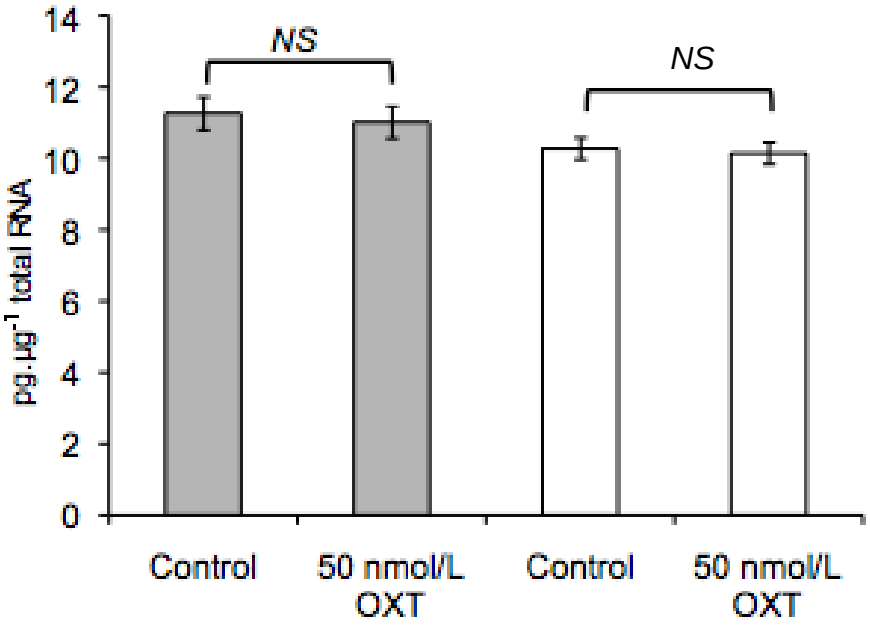
Oxytocin suppresses caveolin-1 expression in PC-3 but not DU 145



Re-expression of PTRF abolishes inhibitory effect in PC-3

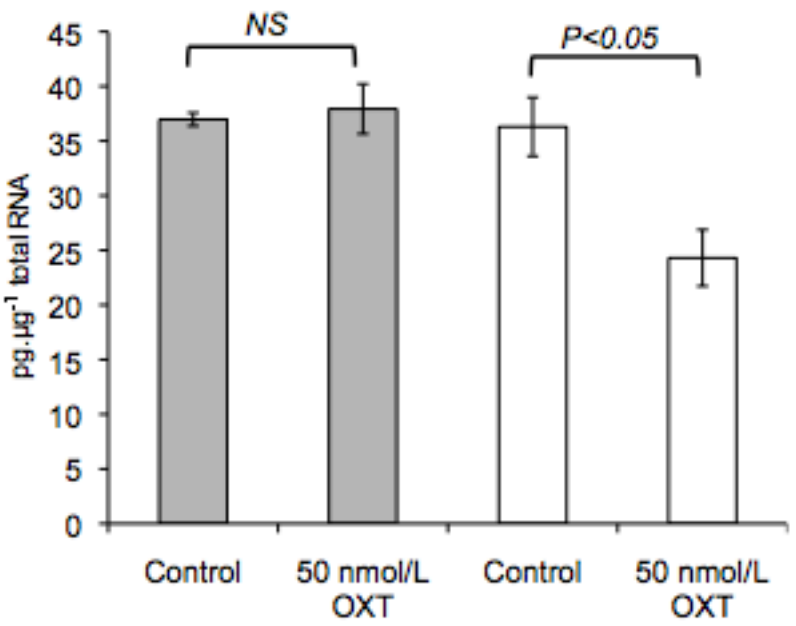
Knockdown of PTRF has no effect on response to OXT in DU145

misense siRNA | PTRF siRNA

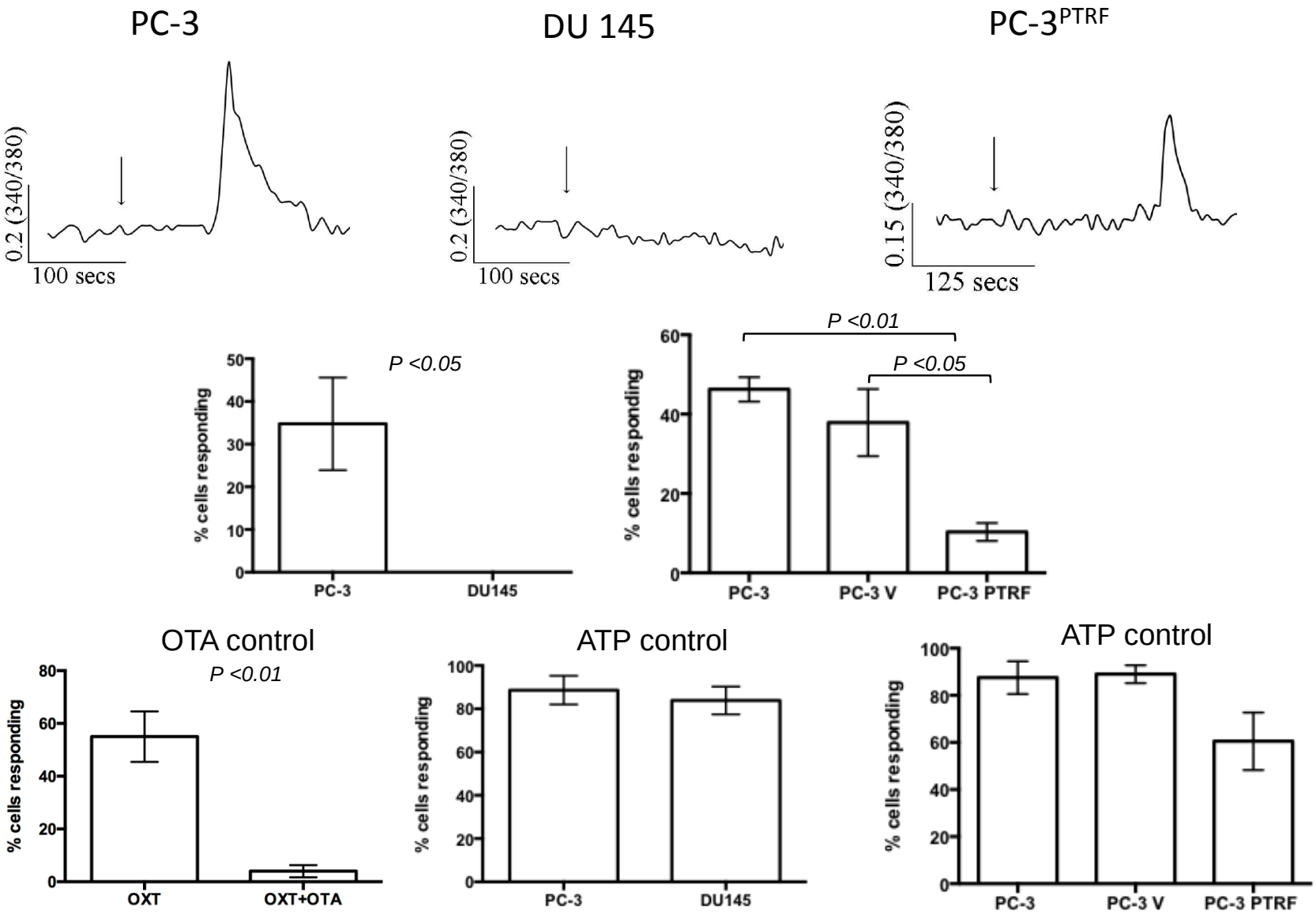


Re-expression of PTRF abolishes OXT inhibition of *CAV1* in PC-3

PC-3^{+PTRF} | PC-3^{+GFP}

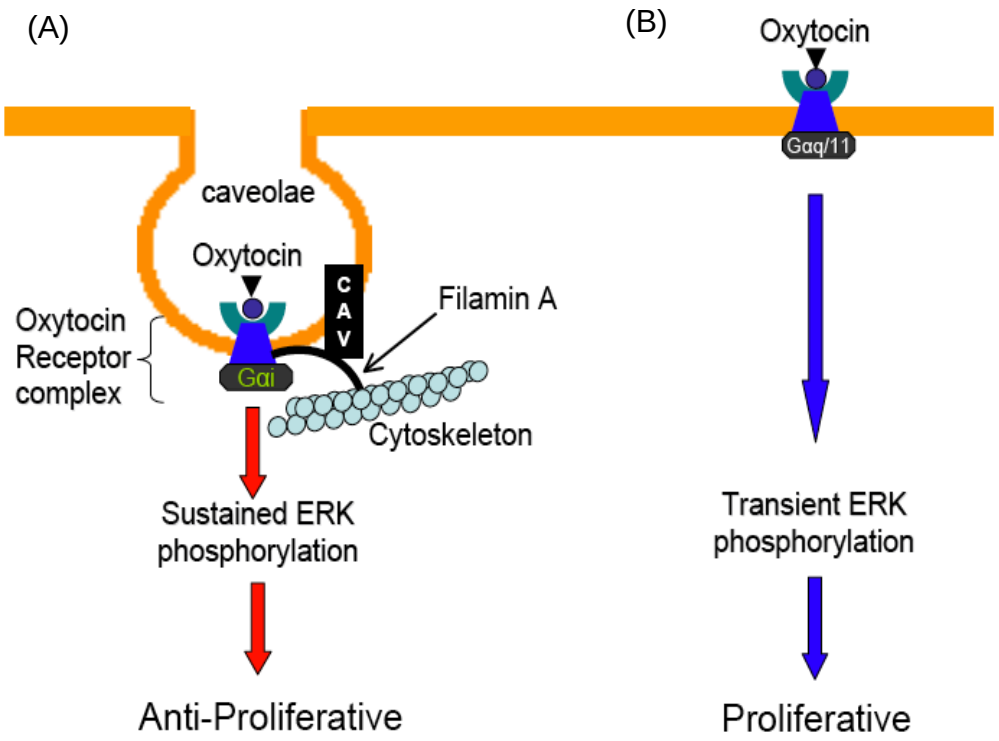


Oxytocin evokes Ca_i^{2+} release in PC-3 but not DU 145 or PC-3^{PTRF}



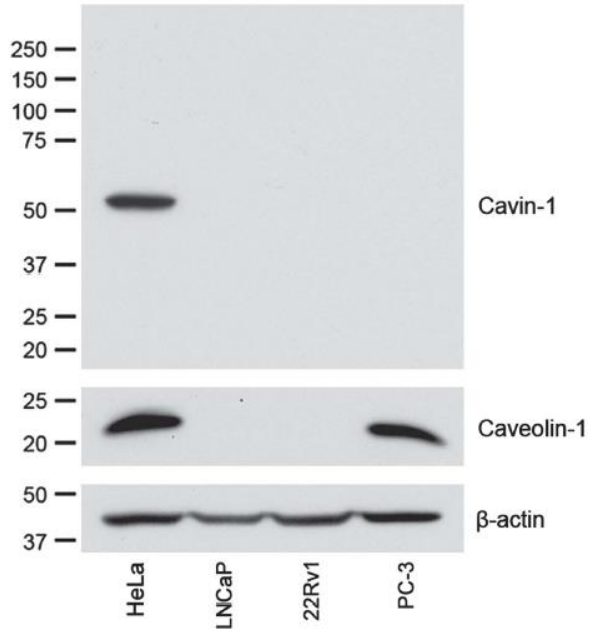
Two hypotheses for differential effects:

1. Different receptor localisation
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From: Assinder (2010) Oxytocin in the Pathophysiology of Prostate Cancer. In: Handbook of Oxytocin Research: Synthesis, Storage and Release, Actions and Drug Forms. (Eds Jastrow H, Feuerbach D). Nova Science, NY. Chapter 7 pp. 157-170.

LNCaP lack PTRF (Cavin-1) and do not form caveolae either

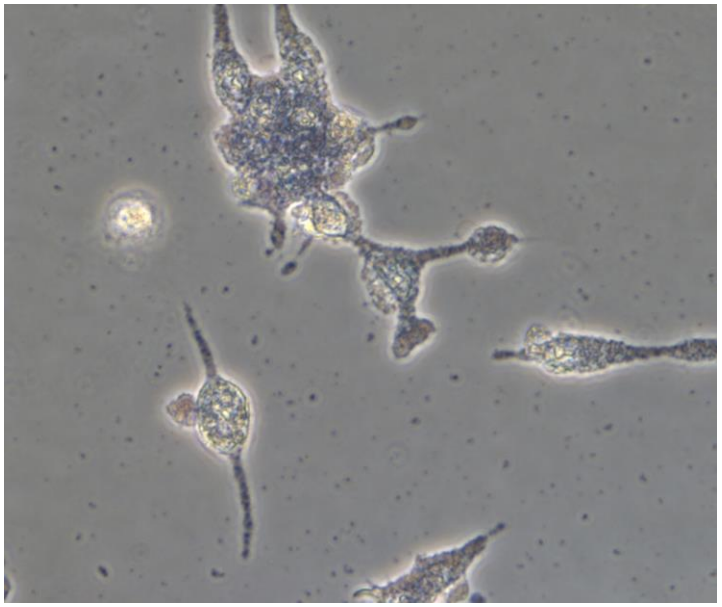


Moon et al. (2014) Oncogene 33: 3561-3570

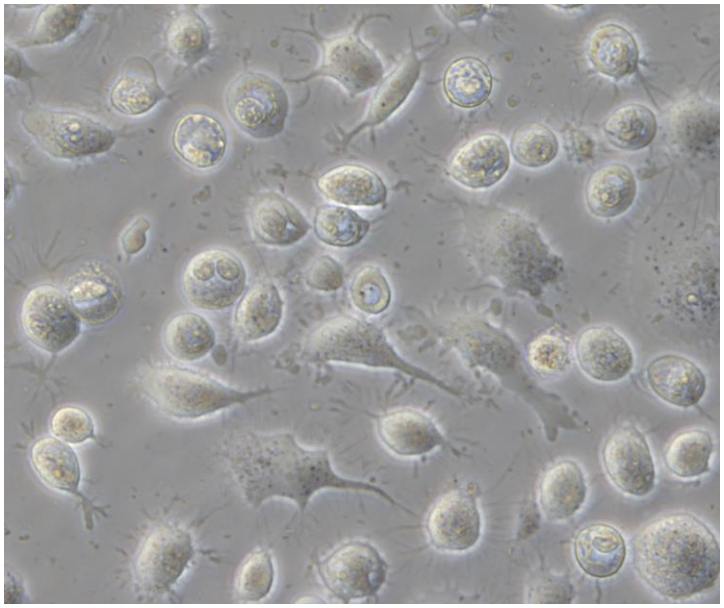
Differential effects of oxytocin on steroidogenic enzymes is evident

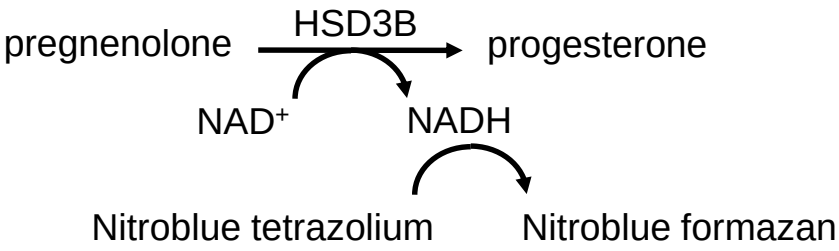
Live cell colourimetric assay for HSD3B and SRD5A

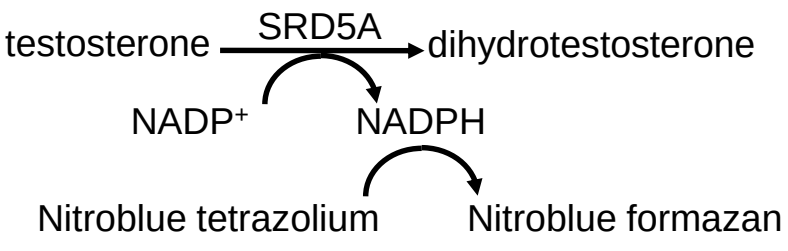
LNCaP HSD3B



PC-3 SRD5A

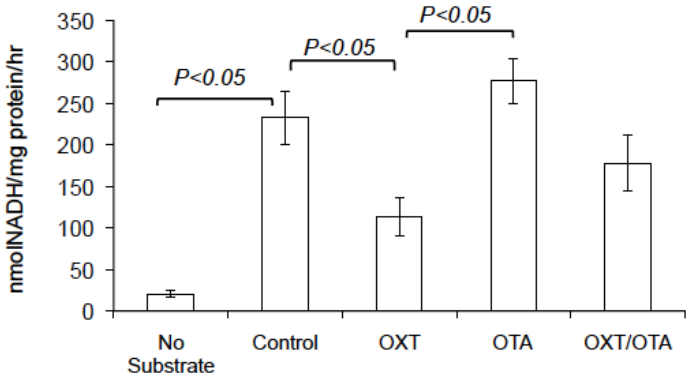




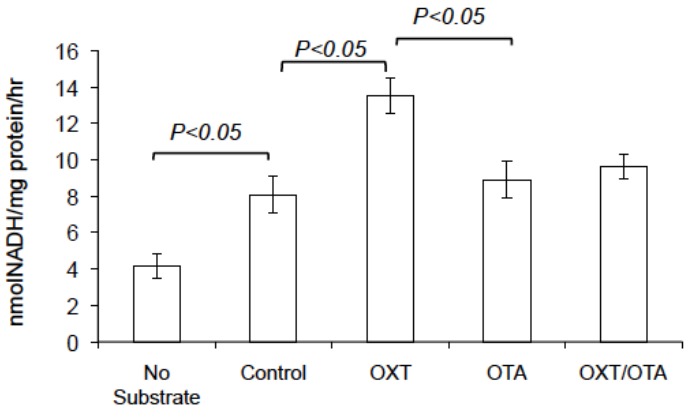


Oxytocin inhibits HSD3B activity in LNCaP, but increases activity in PC-3

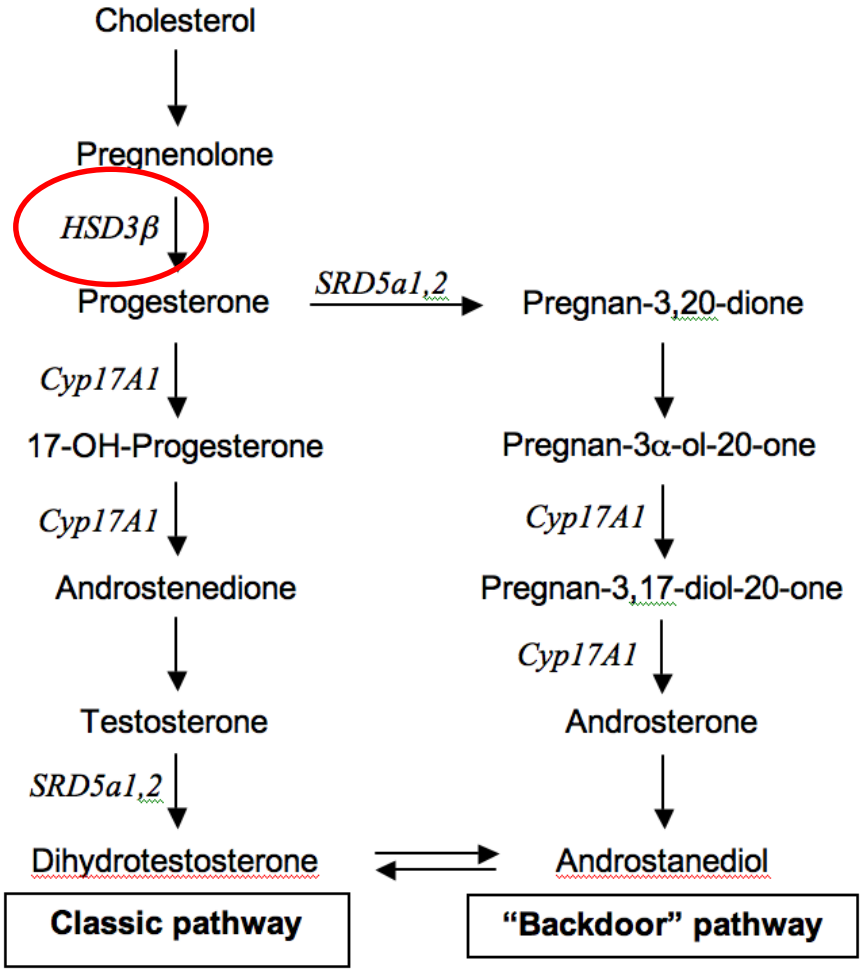
LNCaP



PC-3

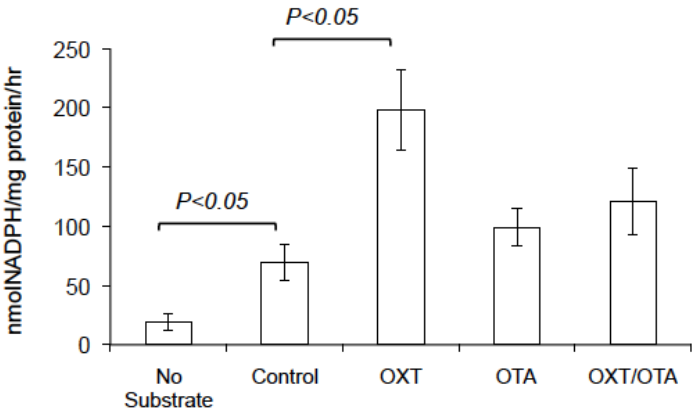


De novo steroidogenesis in PCa

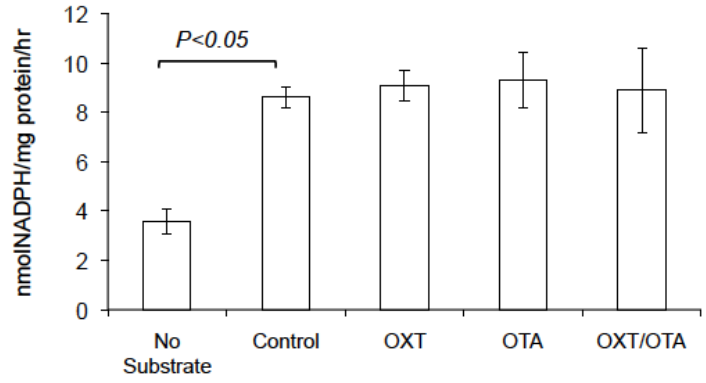


Oxytocin increased SRDA activity in LNCaPs, but decreases activity in PC-3s

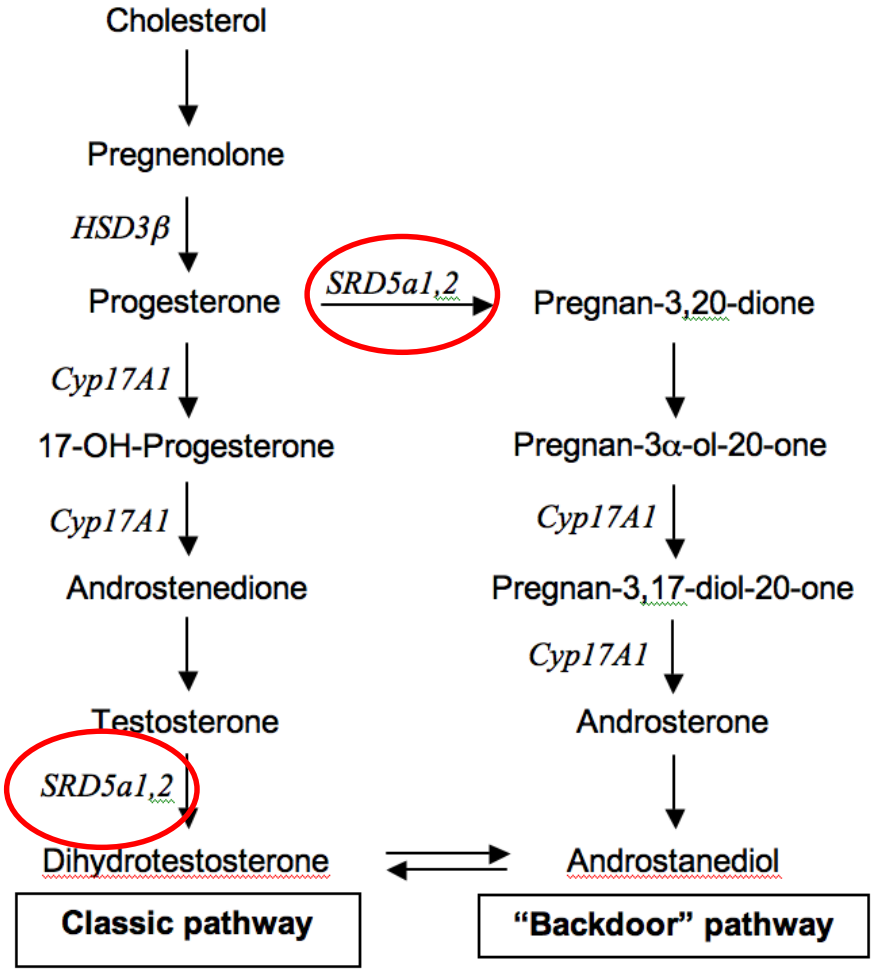
LNCaPs



PC-3s

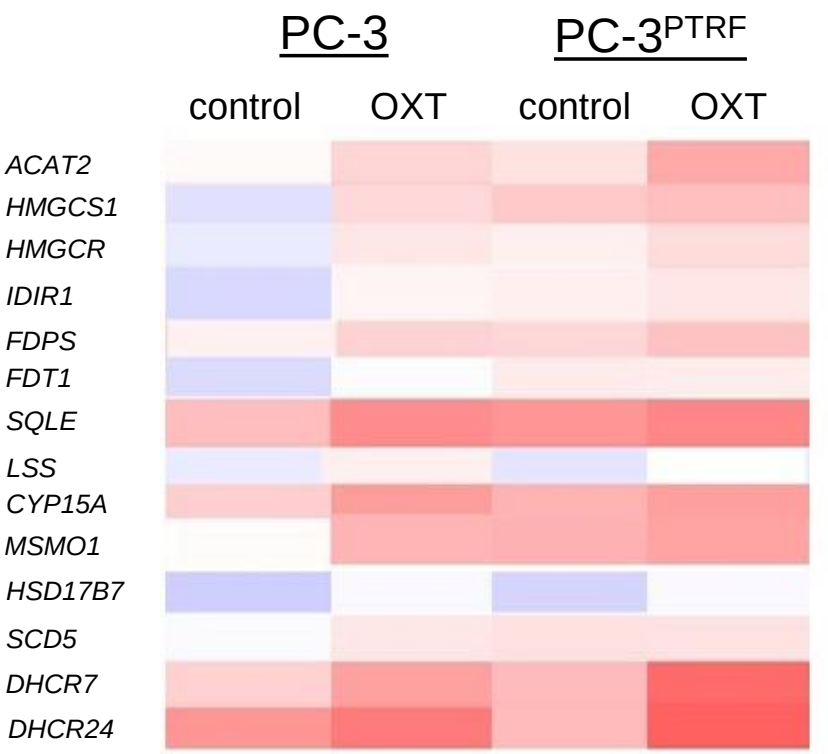


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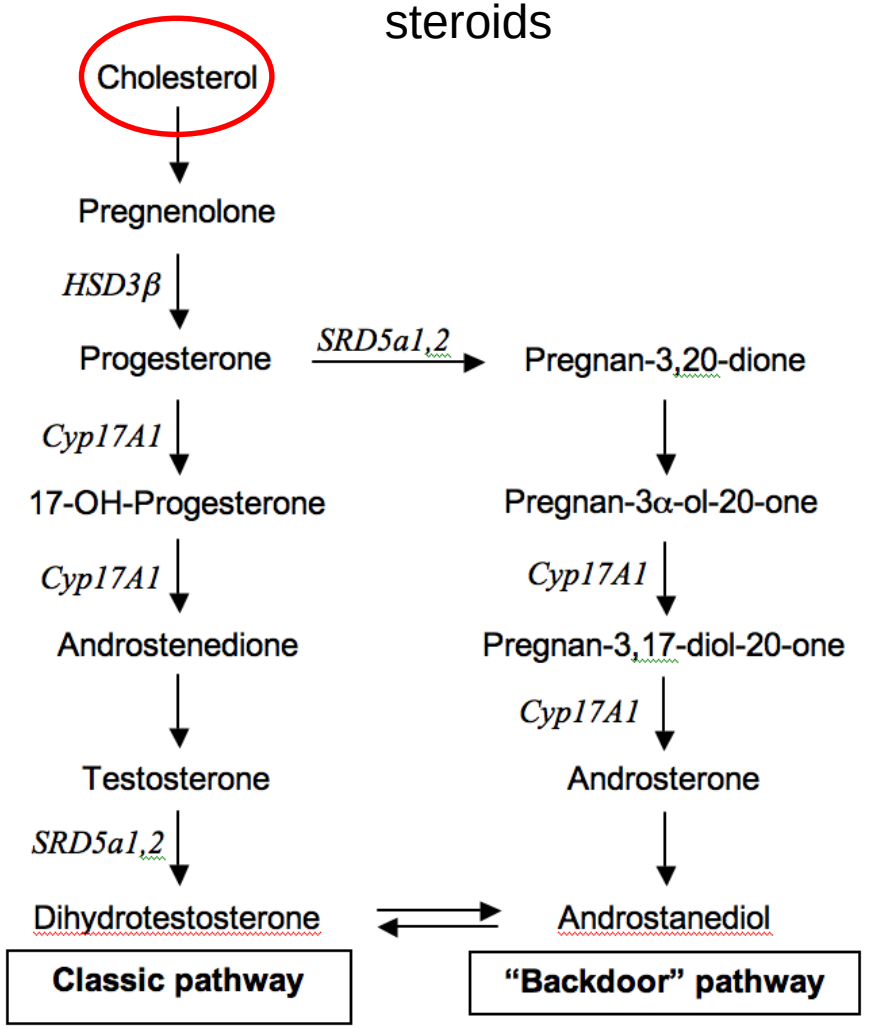


A mixed model of different receptor localisation and different Gα subunits coupling

Oxytocin increases expression of cholesterol biosynthesis genes

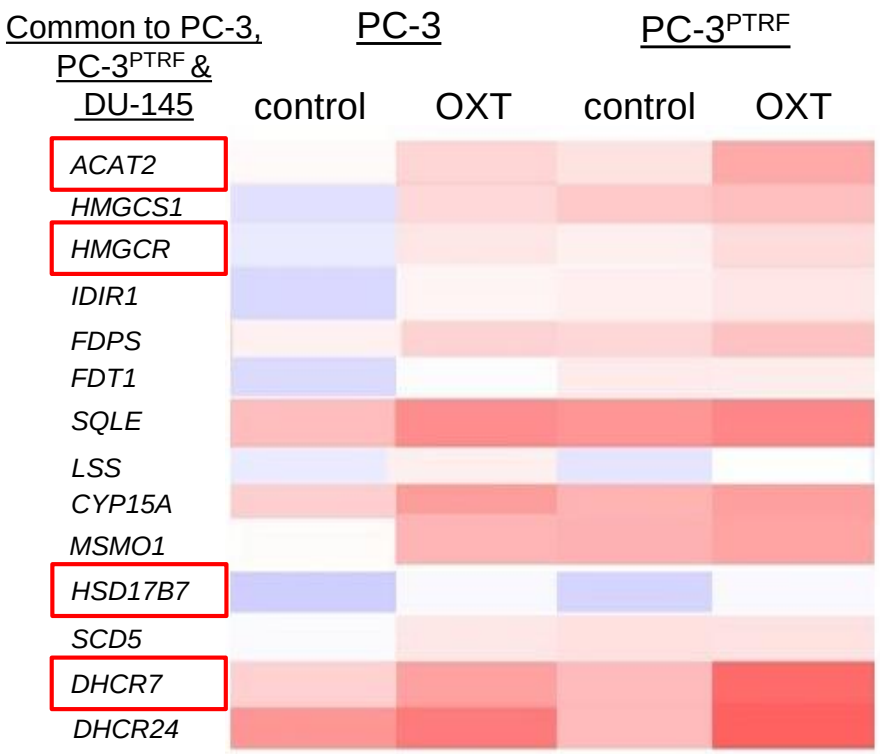


Cholesterol is the precursor of all steroids

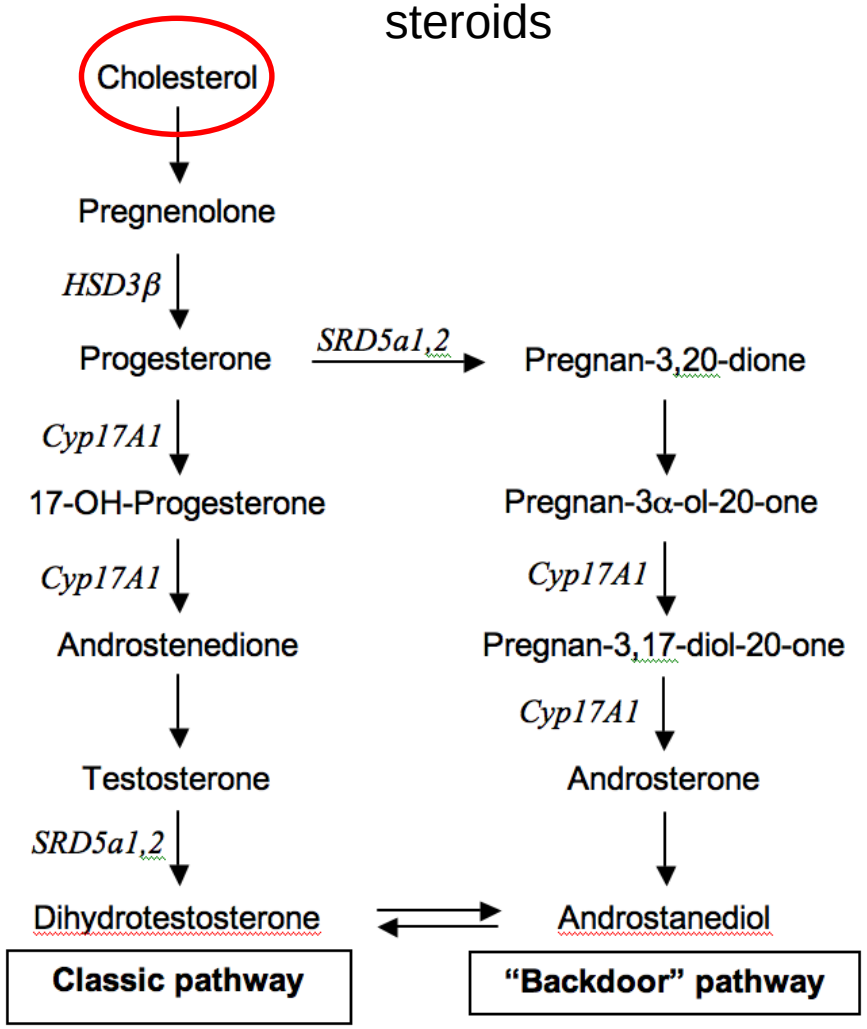


Different G-protein coupling

HMGCR transcript increased by oxytocin in PC-3, PC-3^{PTRF} and DU 145



Cholesterol is the precursor of all steroids



SUMMARY

- Oxytocin signalling is likely determined by both G protein availability and caveolae formation.
- Oxytocin has differential effects according to cell type.
- Oxytocin affects *de novo* steroidogenesis and cholesterol availability.
- Implications for pharmaceutical use?

Acknowledgements

Prof Helen Nicholson, Bristol and Otago University

Dr Kate Whittington, Bristol University

Dr Michelle Hill, University of Queensland

Dr Margot Day, University of Sydney

Alex Cole

Kathryn Davis

Nicole Tom

Dr Stuart Fraser & Blood Cell and Development Lab, University of Sydney

Two hypotheses for differential effects:

Different receptor localisation

Different amounts Gα subunits coupled to the OXTR

