Novel imaging techniques reveal disturbed function of prostate ducts by alpha1-adrenergic receptor blockers but not by PDE5-inhibitors in the treatment of BPH

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INTRODUCTION

- Inhibitors of phosphodiesterase type 5 (PDE5) such as sildenafil and tadalafil relax smooth muscle cells (SMCs) and have emerged as alternative treatment options for benign prostate hyperplasia (BPH).
- Classical treatment of BPH with α_1-adrenergic blockers like tamsulosin often results in side effects like ejaculation disorders.
- The prostate **(Fig.1A)** consists of single glands **(Fig.1A, I)** which produce the prostatic fluid. Excretory ducts **(Fig.1A, II)** transport the fluid to the urethra **(Fig.1A, III)** during the emission phase of ejaculation.
- Most recently, we found spontaneous contractions in isolated prostatic glands **(Fig.1B)** that can be inhibited by the PDE5 inhibitors sildenafil and tadalafil (Kügler et al., FASEB J,2017).
- Comparison of different drug treatments was also performed for seminal vesicles **(Fig.1C)** and the distal part of the epididymis **(Fig.1D)**.

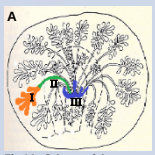

Fig.1A: Scheme of the prostate
I: glands, II: single duct, III: urethra

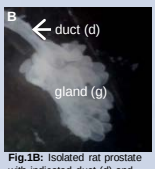

Fig.1B: Isolated rat prostate with indicated duct (d) and glands (g)

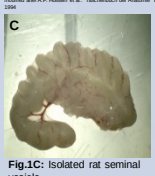

Fig.1C: Isolated rat seminal vesicle

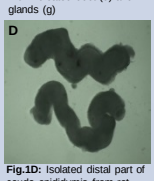

Fig.1D: Isolated distal part of cauda epididymis from rat

AIM

To elucidate and visualize effects of PDE5 inhibitors on contractility of prostatic ducts, seminal vesicles and cauda epididymis in comparison to α_1-adrenergic blockers with its known ejaculation disorders.

RESULTS

Figure 2: Area changes in contractility studies in prostate ducts

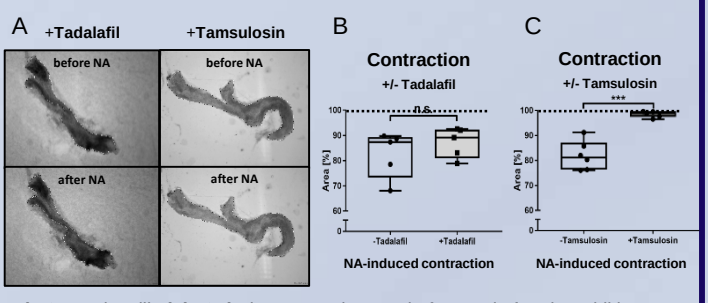

Fig.2: Movie stills **(Fig.2A)** show area changes before and after the addition of NA and was compared for tadalafil and tamsulosin pre-treated prostatic ducts.
Statistics show that tadalafil **(Fig.2B)** does not change contractile patterns of prostatic ducts induced by NA, but tamsulosin **(Fig. 2C)** does.

Figure 3: Contraction frequency of epididymis

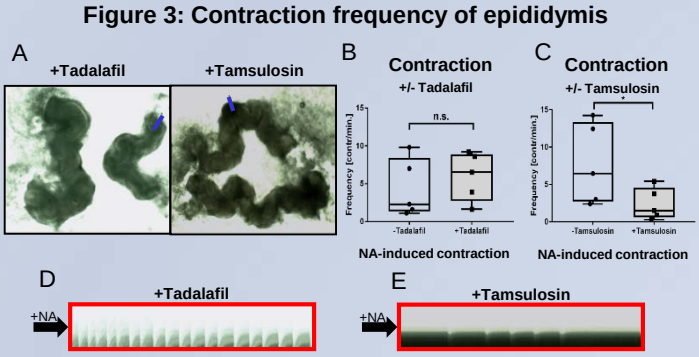

Fig.3: Reslices **(blue line)** according to Snapshots **(Fig. 3A)** allowed analysis of contraction frequencies after addition of NA **(Fig.3D, 3E, red boxes)** for tadalafil **(Fig.3D)** and tamsulosin **(Fig.3E)** pre-treated distal part of cauda epididymis.
Statistical analysis of tadalafil **(Fig.3B)** pre-treated tissue show no significant differences in NA-induced contraction frequency compared to control.
Tamsulosin **(Fig.3C)** pre-treated tissue shows a significant decrease in NA-induced contractions.

RESULTS

Figure 4: Weight changes in contractility studies in seminal vesicles

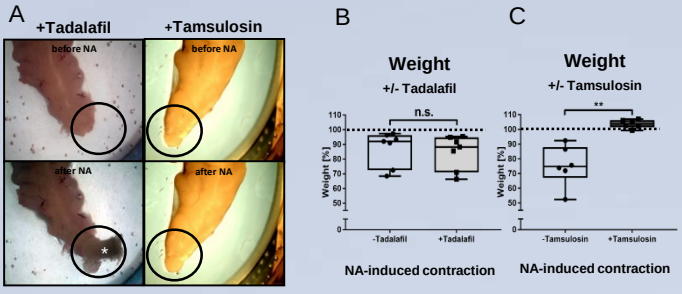

Fig.4: Weight changes of tadalafil and tamsulosin seminal vesicles were compared after NA-induced contractions.
Movie stills show that in the presence of tadalafil **(Fig.4A, +Tadalafil,*)** expulsion of secretion is not disturbed, while an absence of secretion is observed in tamsulosin pre-treated tissue **(Fig.4A, +Tamsulosin)**.
Statistics show no significant weight changes for tadalafil pre-treated tissue after addition of NA compared to control **(Fig.4B)**, but for tamsulosin **(Fig.4C)**.

Figure 5: Area changes in contractility studies in seminal vesicles

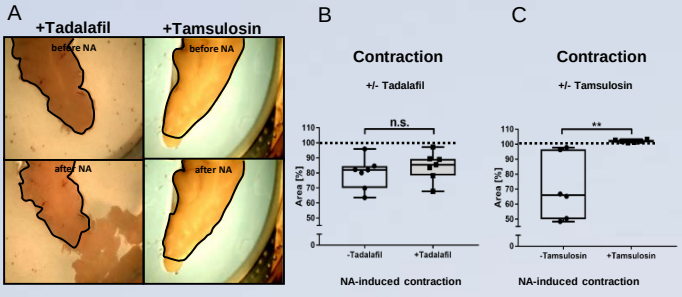

Fig.5: Snapshots **(Fig.5A)** show area changes of tadalafil and tamsulosin pre-treated seminal vesicles before and after NA-induced contractions.
Statistics show no significant differences in contractions regarding area changes after NA-induced contraction for tadalafil **(Fig.5B)** but significant differences for tamsulosin **(Fig.5C)** pre-treated seminal vesicles compared to control.

CONCLUSION

Data suggest that PDE5 inhibitors do not disturb expulsion of prostate and seminal vesicle secretions during ejaculation and contribute to explain adverse effects on ejaculation observed with α_1-adrenergic antagonists.

REFERENCES

Kügler R*, Mietens A*, **Seidensticker M***, Tasch S, Wagenlehner FM, Kaschtanow A, Tjahjono Y, Tomczyk CU, Beyer D, Risbridger GP, Exintaris B, Ellem SJ, Middendorff R: *Novel imaging of the prostate reveals spontaneous gland contraction and excretory duct quiescence together with different drug effects*, FASEB J. 2017 Oct 31doi: 10.1096/fj.201700430R, *equal contribution

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