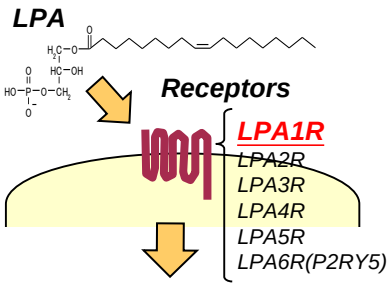
The Effect of ASP6432, a Novel Type 1 Lysophosphatidic Acid Receptor Antagonist, on Urethral Function and Prostate Cell Proliferation

Sakamoto K[1], Noguchi Y[1], Ueshima K[1], Yamakuni H[2], Ohtake A[1], Sato S[1], Ishizu K[1], Hosogai N[1], Kawaminami E[1], Takeda M[1] and Masuda N[1]
1. Astellas Pharma Inc., 2. Astellas Research Technologies Co., Ltd

Background, Aim, Materials and Methods

- Pharmacotherapy for BPH still remains room for improvement.
- Lysophosphatidic acid (LPA) is a bioactive phospholipid reported to contract urethra[1] and proliferate prostate cells[2]. However, details including responsible receptor have not been fully elucidated.
- We explored the role of LPA and type 1 LPA receptor (LPA1R) on urethral and prostatic functions using ASP6432, a newly discovered LPA1R antagonist.
  - Antagonist assays using cells expressing human LPA1R to LPA5R
  - Contraction study in prostate and urethral strips isolated from rats
  - Urethral pressure measurement in anesthetized rats (urethane, 1.2 g/kg ip)
  - Cell proliferation assay [Bromodeoxyuridine (BrdU) incorporation] in primary cultured human prostate stroma cells (PrSC)

[1]Saga et al., PLoS One. 2014;9(4):e93230. [2]Adolfsson et al., Prostate. 2002;51(1):50-8.



- *Smooth muscle contraction*
- *Cell proliferation and survival*
- *Mechanical stress response enhancement*
- *Afferent nerve activation*

Results

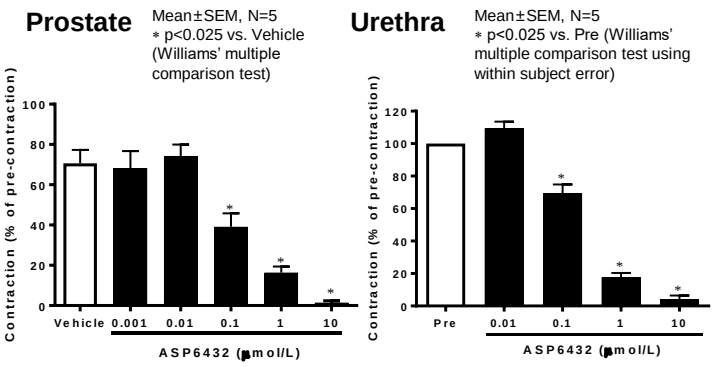
ASP6432 exhibited a potent antagonistic activity on LPA1R with >10 times selectivity over other LPA receptor subtypes.

Effects of ASP6432 on LPA-induced increase in intracellular Ca^{2+} (LPA1R to 4R) or cyclic AMP (LPA5R)

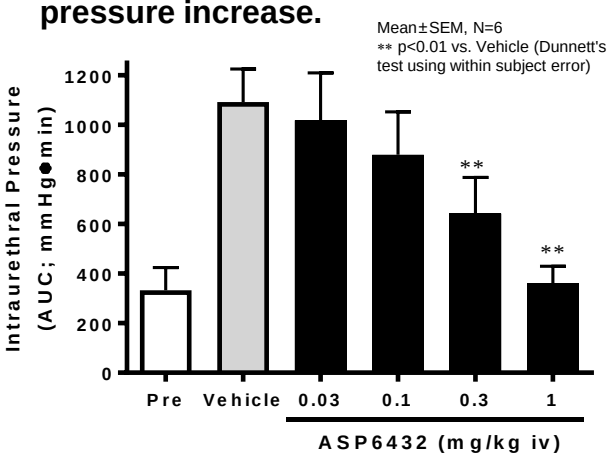
Subtypes	LPA1R	LPA2R	LPA3R	LPA4R	LPA5R
IC_{50} value (nmol/L)	**11**	**> 10000**	**> 10000**	**113.9**	**>30000**

Mean of 2 to 4 independent experiments

ASP6432 concentration-dependently inhibited LPA (100 µmol/L)-induced contractions in rat prostate and urethral strips.

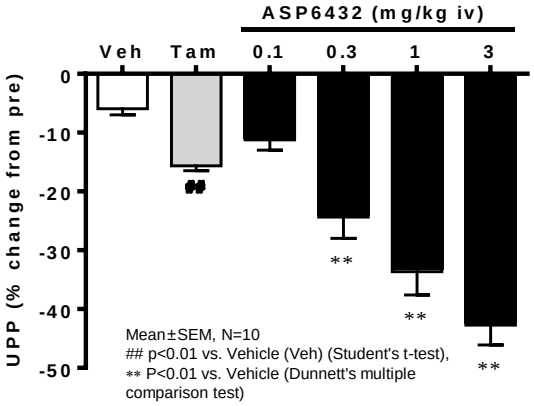


ASP6432 dose-dependently inhibited LPA (3 mg/kg iv)-induced intraurethral pressure increase.

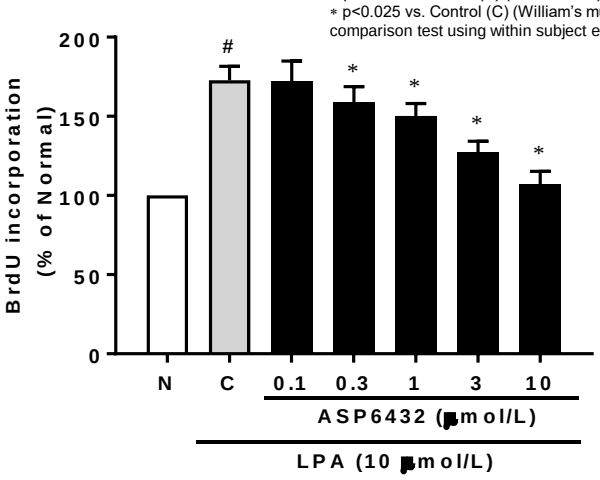


ASP6432 dose-dependently decreased urethral perfusion pressure (UPP) with a maximum reduction (42.5%) larger than that with a sufficient dose of tamsulosin[3] (Tam, 15.4% at 10 µg/kg iv), an α1 adrenoceptor antagonist.

[3]Akiyama et al., J Pharmacol Exp Ther. 1999;291(1):81-91.



ASP6432 suppressed LPA (10 µmol/L)-induced human prostate stromal cell proliferation.



Discussions and Conclusions

- ASP6432 suppressed LPA-induced prostatic/urethral contractions and prostate cell proliferation, indicating the responsible role of LPA1R in these LPA-induced biological responses.
- ASP6432 decreased the urethral perfusion pressure (=baseline urethral pressure under no exogenous LPA stimulation) to a greater extent than that of tamsulosin, suggesting a significant role of LPA and LPA1R in the regulation of urethral tonus.
- With a potent urethral relaxation effect and its potential on prostatic stromal growth inhibition, ASP6432 could be a novel therapeutic agent for BPH.

astellas

Disclosure statement: all authors are employees of the Astellas group.