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

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Background, Aim, Materials and Methods

- Pharmacotherapy for BPH still remains room for improvement.
- Lysophosphatidic acid (LPA) is a bioactive phospholipid reported to contract urethra1 and proliferate prostate cells2. 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
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  - Cell proliferation assay [Bromodeoxyuridine (BrdU) incorporation] in primary cultured human prostate stroma cells (PSC)

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

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

ASP6432 dose-dependently decreased urethral perfusion pressure (UPP) with a maximum reduction (42.5%) larger than that with a sufficient dose of tamsulosin3 (Tam, 15.4% at 10 μg/kg iv), an α1 adrenoceptor antagonist.

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

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

Discussions and Conclusions

- ASP6432 suppressed LPA-induced prostatic/urethral contractions and prostatic 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.

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