

THE EFFECT OF ASP6432, A NOVEL TYPE 1 LYSOPHOSPHATIDIC ACID RECEPTOR ANTAGONIST, ON URETHRAL FUNCTION AND PROSTATE CELL PROLIFERATION

Hypothesis / aims of study

Lower urinary tract symptoms associated with benign prostate hyperplasia (LUTS/BPH) is a common disease condition in elderly men. Although a variety of treatment options have been available, there still remains room for the improvement of clinical efficacy. Lysophosphatidic acid (LPA) is a category of phospholipids produced in multiple organs including prostate. LPA is known to have various physiological functions such as smooth muscle contraction or cell proliferation via G-protein-coupled receptors. However, its functional role and responsible receptor subtype in lower urinary tissues have not been fully elucidated.

In the present study, we investigated the effect of ASP6432, a novel antagonist for type 1 LPA receptor (LPA1R), on urethral contractile function and prostate cell proliferation.

Study design, materials and methods

Antagonistic activity of ASP6432 on LPA1R and other subtypes was investigated using cell lines expressing each LPA receptor subtype. The effect of ASP6432 on the contraction of prostate and urethral smooth muscle induced by LPA (100 μ mol/L) was studied using isolated prostate and urethral strips from rats. The effect of ASP6432 on LPA (3 mg/kg iv)-induced elevation of intraurethral pressure and that on urethral perfusion pressure (UPP) (without LPA stimulation) were evaluated using rats anesthetised with urethane (1.2 g/kg ip). The effect of ASP6432 on LPA (10 μ mol/L)-induced proliferation of human prostate stromal cells was assessed by measuring the incorporation of bromodeoxyuridine (BrdU).

Results

ASP6432 exhibited a potent antagonistic activity on LPA1R with selectivity over other LPA receptor subtypes by more than ten times (Table 1). In the prostate and urethral strips isolated from rats, ASP6432 inhibited the contractions induced by LPA in a concentration dependent manner (Figure 1). In anesthetised rats, ASP6432 dose dependently inhibited LPA-induced elevation of intraurethral pressure (Figure 2). ASP6432 also decreased UPP maximally by around 43%. The reduction of UPP with tamsulosin (10 μ g/kg iv), an α 1 adrenoceptor antagonist, was around 15% (Figure 3). In human prostate stromal cells, the incorporation of BrdU induced by LPA was suppressed with ASP6432 (Figure 4).

Interpretation of results

ASP6432 exhibited a potent antagonistic effect on LPA1R, confirming its applicability in investigating the physiological role of LPA1R in lower urinary tract tissues.

The inhibition of LPA-induced contraction with ASP6432 in isolated prostate and urethral smooth muscle strips indicates that LPA1R is involved in the contractile response stimulated by LPA. In the *in vivo* studies, ASP6432 decreased not only LPA-induced elevation in intraurethral pressure but urethral pressure with no exogenous LPA stimulation. Notably, the maximum reduction of UPP was larger than that of tamsulosin at 10 μ g/kg iv which was three times higher than the dose reported to almost completely inhibit phenylephrine-induced urethral pressure elevation (3 μ g/kg iv; Akiyama et al., 1999). These results indicate that LPA is one of the key physiological regulators of urethral contractile functions through LPA1R.

ASP6432 also inhibited the proliferation of prostate stromal cells induced by LPA. This finding raises the possibility that LPA1R antagonist could inhibit the hyperplasia of prostate stroma observed in BPH on top of the significant urethral relaxation, and thus improve both mechanical and functional obstruction of patients in LUTS/BPH.

Concluding message

The present study demonstrates a significant role of LPA1R in the regulation of urethral tonus and proliferation of prostate cells induced by LPA. The potent urethral relaxation effect of ASP6432 compared with tamsulosin and its potential on prostatic stromal growth inhibition suggest that ASP6432 can be a novel therapeutic agent for LUTS/BPH.

Table1. Antagonistic Effect of ASP6432 on Human LPA Receptor Subtypes

Subtypes	LPA ₁	LPA ₂	LPA ₃	LPA ₄	LPA ₅
IC ₅₀ value (nmol/L)	11	> 10000	> 10000	113.9	>30000

Figure 1. Inhibitory Effect of ASP6432 on LPA-induced Contractions in Isolated Rat Prostate and Urethra

A. Prostate

B. Urethra

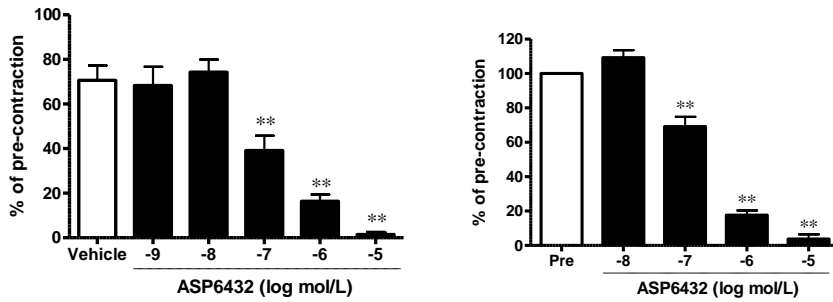


Figure 2. Inhibitory Effect of ASP6432 on LPA-induced Intraurethral Pressure Elevation in Anesthetized Rats

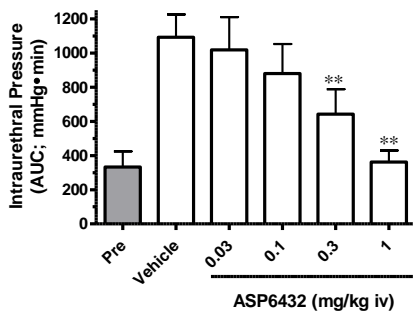


Figure 3. Effect of ASP6432 and Tamsulosin (Tam, 10 µg/kg iv) on Urethral Perfusion Pressure in Anesthetized Rats

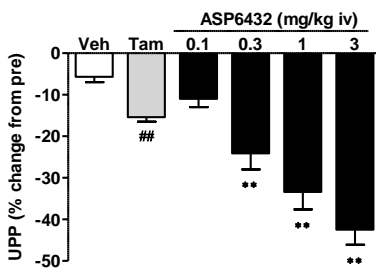
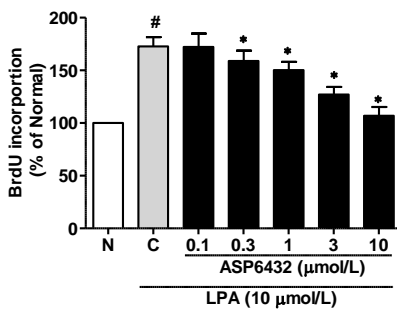


Figure 4. Inhibitory effect of ASP6432 on LPA-induced BrdU Incorporation in Human Prostate Stromal Cells



References

1. Akiyama K, Hora M, Tatemichi S, Masuda N, Nakamura S, Yamagishi R, et al. KMD-3213, a

Disclosures

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