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THE A1A-AR PARTIAL AGONIST, R1484 EXHIBITS SELECTIVITY FOR URETHRAL SMOOTH MUSCLE OVER VASCULAR SMOOTH MUSCLE

Hypothesis / aims of study

The sympathetic outflow from the rostral lumbar spinal cord provides noradrenergic excitatory input to the bladder neck and proximal urethra that is mediated through α_{1A} adrenoceptors (ARs). Activation of α_{1A}-ARs results in increased urethral smooth muscle tone. One of the challenges in using α_{1A}-AR agonists for the treatment of SUI is the ability to achieve a desirable increase in urethral smooth muscle tone while sparing cardiovascular function. Previously it has been shown that moderate intrinsic efficacy at the α_{1A}-AR subtype using the partial agonist, RO1151240, allows for increases in urethral tone while minimizing cardiovascular interference [1]. The purpose of this study was to compare the effects of the weaker α_{1A} partial agonist (Table 1), R1484, to RO1151240 on intra-urethral pressure (IUP) and mean arterial pressure (MAP) in the anesthetized rabbit model. It is hypothesized that with reduced potency at the α_{1A}-AR, selectivity for IUP over MAP can be achieved.

Study design, materials and methods

Female Dutch Belted Rabbits were anesthetized with isoflurane and urethane. The femoral artery and vein were cannulated for the measurement of blood pressure and administration of drug, respectively. The ureters were cannulated to exteriorize the urine. The urethra was cannulated via the external urethral meatus with a water-filled balloon tipped catheter. Two ligatures were made on either side of the balloon to secure the catheter in the urethra proximal to the bladder neck. Amidephrine (0.316μg/kg, i.v.), a selective α_{1A}-AR full agonist, was administered at the start of the experiment as a positive control. One to two hours post amidephrine, vehicle was administered followed by an ascending dose range of R1484 (1-3160 μg/kg, i.v.) or RO1151240 (1-3160μg/kg, i.v.). The drug treated data were normalized to amidephrine and each dose was compared to its pre-dose baseline to determine significant changes in IUP and MAP.

Results

Dose-dependent increases in IUP and MAP at 316, 1000 and 3160 μg/kg ($p< 0.01$) were observed for R1484 (n = 9) with maximum changes at 3160 μg/kg of 44.4% ± 3.73 and 17.5% ± 5.10 for IUP and MAP, respectively as compared to amidephrine. RO1151240 (n = 5) increased IUP at 31.6–1000 μg/kg and significantly increased MAP at 31.6 -1000 μg/kg, dose-dependently. At 1000 μg/kg, the maximum change in IUP and MAP for RO1151240 were 31.9% ± 4.65 and 25.6% ± 2.58 ($p< 0.01$) compared to amidephrine, respectively.

Table 1. Relative agonist properties of standard and novel α_{1A} adrenoceptor agonists

	α_{1A}		α_{1B}		α_{1D}	
Agonist	pEC50	Intrinsic Activity	pEC50	Intrinsic Activity	pEC50	Intrinsic Activity
Norepinephrine	8.34	1.00	9.43	1.00	9.21	1.00
Amidephrine	7.74	1.02	<6	0.31	5.61	0.21
RO1151240	7.16	0.56	<5	0	<5	0
R1484	6.07	0.48	<4	0	<4	0

Data obtained using FLIPR assay assessing Fluo-3 detection of elevations in $[Ca^{2+}]_i$ in CHO cells expressing human recombinant $\alpha_{1A, B, D}$-ARs.

Interpretation of results

Both R1484 and RO1151240 dose-dependently increased IUP and MAP in the anesthetized rabbit. Consistent with partial agonism, both compounds resulted in decreased efficacy in IUP and MAP as compared to the full agonist amidephrine. Changes in IUP and MAP began at 31.6 μg/kg ($0.01 \leq p < 0.05$) for RO1151240 as compared to 316 μg/kg ($p < 0.01$) for R1484. This 10 fold lower potency of R1484 at activating α-1A ARs in the rabbit which is consistent with FLIPR data (Table 1). Both compounds had a reduced effect on MAP (17.5% and 25.6% for R1484 and RO1151240, respectively) versus IUP (44.4% and 31.9%, respectively). Therefore, in the rabbit it appears urethral smooth muscle tone may be more sensitive to α-1A adrenergic stimulation than vascular smooth muscle. However, R1484 had a lesser effect on MAP (17.5%) and a greater effect on IUP (44.4%) when compared to RO1151240 (MAP 25.6%, IUP 31.9%) in the rabbit.

Concluding message

These data illustrate that decreased potency and efficacy may impart increased selectivity for IUP over MAP (i.e. uroselectivity) among α_{1A}-AR agonists and therefore, R1484 may be a useful tool in treating stress urinary incontinence.

1. Pharmacological characteristics of RO 115-1240, a selective α1A/1L-adrenoceptor partial agonist: a potential therapy for stress urinary incontinence, 2004 BJU International, Vol. 93 162-170.