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α1-Adrenergic Receptors and LUTS

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α1-AR antagonists have been shown to relieve obstructive and irritative symptoms in patients with bladder outlet obstruction (BOO) and associated lower urinary tract symptoms (LUTS). α1a-ARs, the predominant α1-AR present in prostate stroma/smooth muscle, are important in the dynamic component (prostate smooth muscle contraction) of benign prostatic hyperplasia (BPH); in contrast, α1b-ARs have been described to predominate in bladder and spinal cord. In determining the functional significance of each α1-AR subtype in treating LUTS, careful analysis of symptom relief with selective α1-AR antagonists is revealing. Highly selective α1a-AR antagonists relax prostate smooth muscle and increase urine flow, but do not improve LUTS symptoms, whereas combined α1a/α1b-AR antagonists and non–subtype selective antagonists are effective. This suggests that while blockade of α1a-ARs remains important in relieving BOO, LUTS treatment requires α1b-AR blockade either directly or indirectly. Absent in LUTS symptom treatment is the α1b-AR; interestingly, because α1b-ARs are increasingly important in vessel tone with age, avoiding antagonism of this subtype when treating LUTS may be clinically important in elderly patients. The role of bladder α1a-ARs in LUTS is emphasized by animal studies where bladder α1a-ARs increase relative to other subtypes in the presence of BOO. Supporting this finding is a recent functional whole animal study suggesting that the α1b/α1a-AR antagonist tamsulosin decreases urinary frequency after 6 weeks BOO, whereas 5-methylurapidil (an α1a antagonist) does not. In translating these findings to humans, one recently published study suggests α1-AR subtypes do not change with BOO, whereas another study carefully dissecting human detrusor in patients with/without LUTS supports the animal findings in suggesting an important role of the α1b-AR. In spite of recent advances in LUTS, the precise mechanism underlying relief of LUTS symptoms remains unknown. However, intermittent hypoxia may regulate many bladder genes, including modulation of α1-AR subtypes.

Currently 7 α1-AR antagonists are available for use in treating LUTS in humans in various parts of the world. These drugs include non–subtype selective blockers alfuzosin, doxazosin, prazosin, and terazosin, as well as subtype selective blockers tamsulosin (α1 = α1a > α1b-AR), naftopidil (α1b > α1a > α1b-AR), and silodosin (α1a > α1a > α1b-AR). All 7 drugs are efficacious in terms if increased urine flow (relief of outlet obstruction) compared to placebo, demonstrating clinically the effect of relaxing prostate smooth muscle via blockade of α1b-ARs. All have positive effects in terms of symptom scores for bladder irritability symptoms, demonstrating the effect clinical blockade of bladder α1b-ARs. Hypotensive side effects are less for the subtype–selective drugs in elderly men where vascular α1b-ARs are relatively up–regulated. Another important class side effect, mediated via α1a-AR blockade, includes intra–operative floppy iris syndrome (IFIS). Elderly patients undergoing cataract surgery should discontinue α1a-AR antagonists 2 weeks prior to surgery in order to avoid a small pupil and iris blowing, classic symptoms of IFIS.

In summary, LUTS remains a serious urologic problem with complex pathophysiology. Understanding the role of α1-AR subtypes in this disease remains important.