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 α_1 -Adrenergic Receptors and LUTS

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α_1 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). α_{1a} ARs, the predominant α_1 AR present in prostate stroma/smooth muscle, are important in the dynamic component (prostate smooth muscle contraction) of benign prostatic hyperplasia (BPH); in contrast, α_{1d} ARs have been described to predominate in bladder and spinal cord. In determining the functional significance of each α_1 AR subtype in treating LUTS, careful analysis of symptom relief with selective α_1 AR antagonists is revealing. Highly selective α_{1a} antagonists relax prostate smooth muscle and increase urine flow, but do not improve LUTS symptoms, whereas combined α_{1a}/α_{1d} AR antagonists and non-subtype selective antagonists are effective. This suggests that while blockade of α_{1a} ARs remains important in relieving BOO, LUTS treatment requires α_{1d} AR blockade either directly or indirectly. Absent in LUTS symptom treatment is the α_{1b} AR; interestingly, because α_{1b} 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 α_{1d} ARs in LUTS is emphasized by animal studies where bladder α_{1d} ARs increase relative to other subtypes in the presence of BOO. Supporting this finding is a recent functional whole animal study suggesting that the α_{1a}/α_{1d} AR antagonist tamsulosin decreases urinary frequency after 6 weeks BOO, whereas 5-methylurapidil (an α_{1a} antagonist) does not. In translating these findings to humans, one recently published study suggests α_1 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 α_{1d} 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 α_1 AR subtypes.

Currently 7 α_1 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 ($\alpha_{1a} = \alpha_{1d} > \alpha_{1b}$ AR), naftopidil ($\alpha_{1d} \geq \alpha_{1a} > \alpha_{1b}$ AR), and silodosin ($\alpha_{1a} > \alpha_{1d} > \alpha_{1b}$ AR). All 7 drugs are efficacious in terms of increased urine flow (relief of outlet obstruction) compared to placebo, demonstrating clinically the effect of relaxing prostate smooth muscle via blockade of α_{1a} ARs. All have positive effects in terms of symptom scores for bladder irritability symptoms, demonstrating the effect of clinical blockage of bladder α_{1d} ARs. Hypotensive side effects are less for the subtype-selective drugs in elderly men where vascular α_{1b} ARs are relatively up-regulated. Another important class side effect, mediated via α_{1a} AR blockade, includes intra-operative floppy iris syndrome (IFIS). Elderly patients undergoing cataract surgery should discontinue α_{1a} 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 α_1 AR subtypes in this disease remains important.