Male lower urinary tract symptoms and α_{1D}-adrenoceptors

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ABBREVIATIONS AND ACRONYMS

AR = adrenoceptor

LUTS = lower urinary tract symptom

mRNA = messenger ribonucleic acid

BOO = bladder outlet obstruction

SHR = spontaneous hypertensive rat

KO = knock out

WT = wild type

ATP = adenosine 5'- triphosphate

BPO = benign prostatic obstruction

FDV = first desired volume

SDV = strong desired volume

FVC = frequency volume chart

PFS = pressure flow study

IPSS = international prostate symptom score

RT-PCR = reverse transcriptase polymerase chain reaction

OVX = ovariectomy

TRPM8 = transient receptor potential channel melastatin member 8

ABSTRACT

Historically, α_1-adrenoceptors have been classified into 3 subtypes (α_{1A}, α_{1B}, and α_{1D}) that are widely distributed in various organs. Research on the α_{1D}-adrenoceptors in the bladder, urethra, and prostate has focused on the relationship between expression levels and symptoms of bladder outlet obstruction, and the implications and functional roles of α_{1D}-adrenoceptors subtypes in these organs. The α_{1D}-adrenoceptor mRNA and protein seem to be increased in obstructed bladders or small capacity bladders. On the other hand, α_{1D}-adrenoceptor subtype knock-out mice have been found to have a prolonged voiding interval. Interestingly, an α_{1D}-adrenoceptor antagonist was found to inhibit the facilitation of afferent nerve activity for the micturition reflex induced by intravesical infusion of acetic acid. Clinically, patients who felt urgency at low filling volumes and had a small bladder capacity were found to have more α_{1D}-adrenoceptor mRNA in their bladder mucosa than patients, who felt urgency at high filling volumes and had a large bladder capacity. An α_{1D}-adrenoceptor antagonist was found to increase the first desired volume and the maximum desired volume while decreasing detrusor overactivity in pressure flow studies. Thus, α_{1D}-adrenoceptors in the lower urinary tract may play an important role in the pathophysiology of lower urinary tract disorders.

Keywords: storage symptoms, voiding symptoms, alpha1-adrenoceptor subtypes, voiding dysfunction, bladder

1. BASIC STUDIES

1. 1. α_1 adrenoceptor subtypes

Drugs targeting adrenoceptors (ARs) producing activation and/or inhibition are some of the most widely used therapeutic agents in clinical medicine. ARs bind and are activated by the endogenous catecholamines adrenaline and noradrenaline. α_1-AR subtype cDNAs encoding three α_1-AR subtypes (α_{1A}, α_{1B}, and α_{1D}) have been cloned and characterized pharmacologically.[1-6] The α_{1D}-ARs have been shown to have 10 to 100-fold higher affinity for the endogenous neurotransmitters norepinephrine and epinephrine compared with the α_{1A}- or α_{1B}-AR subtypes.[6] This finding provides a potentially important mechanistic rationale for targeting α_{1D}-ARs when treating lower urinary tract symptoms (LUTS).

1.2. Expression of α_1-AR subtypes in animal models and afferent nerve activity modulation through α_{1D}-ARs in voiding function

In some animal models associated with bladder outflow obstruction (BOO), hypertension and aging have been found to complicate urinary bladder dysfunction.[7-10] In each of these models an elevated expression level of α_{1D}-AR mRNA or α_{1D}-AR protein has been demonstrated (Fig. 1). To counteract these pathological changes, some of which are, at least partly, caused by α_{1D}-AR stimulation, it is reasonable to assume that an α_{1D}-AR antagonist could be useful.

1.2.1. Expression of α_1-AR subtype in animal models

In animal studies, Hampel et al. found that BOO produced a 6-fold increase in bladder weight vs. sham operation, and significantly increased voiding frequency.[11] Although the bladder α_1-AR density did not increase overall, striking changes in α_1-AR subtype expression were demonstrated. In control animals, 70% of α_1-AR mRNA was the α_{1A} subtype, 5% was α_{1B}, and 25% was α_{1D}, whereas in obstructed animal bladders, α_1-AR expression changed to 23% α_{1A}, 2% α_{1B}, and 75% α_{1D}. Changes in α_1-AR mRNA expression were of similar magnitude throughout the bladder dome, mid body, and base. Parallel changes were also evident at the protein level, with 100% α_{1A}-AR expression in control animals changing to 36% (mean value) in animals with a 5-fold or greater increase in bladder weight. The data of Hampel et al. are suggestive, but whether a change in α_{1D} density could have functional consequences was not investigated. However, it has been shown pharmacologically that elevated urinary frequency in obstructed rats was decreased with tamsulosin ($\alpha_{1A/1D}$ antagonist) but not with 5-Me-urapidil (α_{1A} antagonist).[12] Further, Barendrecht et al. reported that relaxation responses to the endogenous agonist noradrenaline through β-AR are turned into α_1-AR-mediated contraction responses in BOO, possibly due to up-regulation of α_{1D}-AR.[10] These findings support the hypothesis that the α_{1D}-ARs are mechanistically involved in the development of storage symptoms, and they are plausible targets for therapeutic interventions to achieve a stable

bladder condition and control storage symptoms. Recently, changes in the distribution of the α_1-AR subtype in the urinary bladder have been demonstrated in a rat BOO model.[13] The study was conducted with a sham group and a BOO group to evaluate the impact of BOO on α_1-AR expression. While there was no major difference in weight between the sham and BOO groups, urinary bladder weight was higher in the BOO group (0.76 g) than in the sham group (0.11g). The expression of α_{1D}-AR subtype was higher in the urothelium in the BOO group than in the sham group. The expression of α_{1A}-AR mRNA was markedly reduced in the BOO group (0.57) compared to the sham group (2.43). In contrast, the expression of α_{1D}-AR mRNA was notably higher in the BOO group (1.79) than in the sham group (0.71). An actual difference in the α_1-AR subtype between the smooth muscle layers and the urothelium could not be detected.

Persson et al. demonstrated that bladder function in spontaneously hypertensive rats (SHRs) differed from that in control rats and was characterized by a decrease in bladder capacity and micturition volume, as well as by an increase in nonvoiding bladder contractions.[7] The results have furthermore suggested differences in smooth muscle and neuronal responsiveness to norepinephrine between SHR and control rats. The distribution of α_1-AR subtype in the urinary bladder of SHRs has been reported; rats were assigned to 2 groups, and the reference group was fed a normal chow diet, while another group was fed experimental chow that contained 8% NaCl.[14] Blood pressure increased slightly depending on the NaCl diet. While the expression of α_{1D}-AR subtype was increased in the

NaCl diet group, the expression of α_{1A}-AR subtype was dramatically decreased in both bladder urothelium and smooth muscle layers. The expression level of α_{1D}-AR mRNA was similarly increased, and that of α_{1A} was decreased. These findings suggest that the dynamics of α_1-AR expression could partly contribute to bladder function.

Using rat bladder, Dmitrieva et al. investigated whether aging affects expression of α_{1D}-AR and whether α_{1D}-AR mediates contraction.[9] Immunofluorescent staining for α_{1D}-AR was detected in sections of the urothelium. Furthermore, Western blotting confirmed more α_{1D}-AR in the urothelium in aged rats than in young rats. Moreover, phenylephrine increased intravesical pressure in a concentration-dependent manner in both young and aged rats, and the effect of phenylephrine was significantly greater in aged than in young rats. It was also found that prazosin and BMY7378, an α_{1D}-AR antagonist, decreased the contractile response induced by phenylephrine in a concentration-dependent manner in aged and young rats. BMY7378 produced significantly greater inhibition in aged rats, while prazosin did not. These findings suggest that α_{1D}-AR was overexpressed in aged rat urothelium, resulting in enhancement of the contractile response.

1.2.2. Voiding function and afferent nerve activity modulation through α_{1D}-AR

To examine whether a molecule is really important in some physiological responses, animal genetic models may have advantages. Two groups recently reported that the α_{1D}-AR subtype plays a

unique role in voiding in α_{1D}-AR knockout (KO) mice. Chen et al. demonstrated that the α_{1D}-AR subtype has an important role in regulating bladder function.[15] Mean daily voiding frequency was significantly lower in α_{1D}-AR KO mice (9 times) than in wildtype (WT) mice (16 times). Mean volume per void was significantly larger in α_{1D}-AR KO mice than in WT mice. Similarly, cystometric analysis demonstrated larger bladder capacity (140%) and voided volume (146%) in α_{1D}-AR KO mice than in WT mice. Moreover, Wang et al. suggested that locally-released noradrenaline activates urothelial α_{1D}-AR and affects urinary bladder function.[16] Cystometry using wild-type mice demonstrated that intravesical infusion of noradrenaline into the urinary bladder shortened the intercontraction interval in a dose-dependent manner, without changing the maximum voiding pressure. In contrast, α_{1D}-AR KO mice showed no change in the intercontraction interval in response to intravesical infusion of noradrenaline. These findings indicate a predominant involvement of α_{1D}-AR in the facilitation of the micturition reflex by noradrenaline.

Ishihama et al. demonstrated that α_{1D}-ARs were expressed in the urothelium of the rat bladder with Western blotting and immunohistochemistry, and that inhibition of these receptors affects reflex voiding through an afferent nerve decrease.[17] The rather selective α_{1D}-AR antagonist naftopidil prolonged the intercontraction interval during continuous infusion cystometrograms in conscious rats (143% of the control value) and suppressed the excitatory effect of intravesical infusion of 0.1% acetic acid on the intercontraction interval (220%). Naftopidil inhibited the bladder afferent nerve

activity induced by bladder distension (32%) and acetic acid infusion (30%) and decreased ATP levels in the bladder perfusate during bladder distention (37%). Sugaya et al. also reported the effects of naftopidil on the urinary ATP level and bladder activity after bladder stimulation in rats using continuous cystometry with 0.1% acetic acid.[18] The shortened interval between bladder contractions with the acetic acid solution was recovered with naftopidil treatment. The urinary ATP level increase caused by the infusion of acetic acid was less with naftopidil. Therefore, naftopidil's inhibitory effect on bladder activity may be partly due to blocking ATP release from the bladder epithelium.

A relationship between sensory nerve activation and an increased voiding reflex response is well known. Cold stress was found to significantly decrease the voiding interval, micturition volume, and bladder capacity in conscious rats.[19] TRPM8 expression on the skin partly mediated the micturition responses.[20] But how does α_{1D}-AR affect the above relationship? A novel and interesting finding associated with cold stress stimulation was recently reported using OVX rats,[21] which have been shown to have a decreased sensory afferent nerve threshold. Cold stress stimulates the skin TRPM8. The TRPM8-positive area in the skin was significantly higher (2-times) in OVX rats than in sham rats. In the OVX rats, the voiding interval was shortened from 3.0 min to 2.0 min, and the bladder capacity was smaller, from 0.73 mL to 0.39 mL under the low temperature condition as compared to the sham rats. Furthermore, naftopidil, an α_{1D}-AR antagonist, blocked the OVX-induced effects

(voiding interval, 4.7 min; bladder capacity, 0.83 mL). Therefore, the increased TRPM8 in OVX rats may result in α_{1D}-AR mediated detrusor overactivity induced by cold stress under afferent nerve activation.

2. CLINICAL STUDIES

2.1. α_1-AR subtypes in the human lower urinary tract

Historically, Malloy et al. found species heterogeneity in α_1-AR subtype expression (human vs. rat), with α_{1D} predominating in human detrusor.[22] Total α_1-AR expression in human bladder was 6 fmol/mg total protein. Although significantly less than the α_1-AR density in human prostate, bladder α_1-AR expression is 3 times higher than the density in the human coronary artery.[23] At a subtype level, α_{1D}-ARs are twice as abundant as α_{1A}-ARs in human detrusor at both the mRNA and protein levels; no α_{1B}-ARs were found in human detrusor. Overall α_{1D}-AR expression in human tissue is more limited than that of other α_1-AR subtypes.[24]

2.2. Functional responses of α_1-AR in obstructed bladder

Nomiya et al. found that α_1-ARs were expressed at low levels in human bladder, and α_{1D}-AR mRNA was increased 1.8 times in obstructed patients compared with the control group, but the difference was not significant.[25] Their functional study showed that phenylephrine at concentrations up to 10^{-4} M produced no contractile response in obstructed or control bladders. However, Chapple et al. showed that an α_1 agonist produced responses in 6 of 11 patients with overactive detrusor bladder specimens.[26] Furthermore, Bouchelouche et al. showed significant contractile responses to phenylephrine in preparations from BOO bladders.[27] In contrast, α_1 agonist responses were slight in

all nonobstructed bladders, although potassium-induced contractions in these tissue strips were similar to those in BOO specimens. Another interesting finding was that phenylephrine induced contractile oscillations and tonic contractions in BOO preparations, while each type of contraction was dose dependently inhibited by tamsulosin. Such inhibition was also obtained with the α_{1D}-AR antagonist BMY7378, by shifting the phenylephrine-induced dose-response curve. These results and previous animal investigations [11] support the hypothesis that α_{1D}-AR might be important in storage symptoms associated with male LUTS.

The correlation between bladder expression of α_1-ARs and sensation in patients has been unclear. A recent investigation demonstrated expression of α_1-AR mRNAs in the bladder mucosa of men with LUTS and BPO and the association of α_1-AR mRNAs with urodynamic parameters during storage of experimentally infused contrast medium.[28] Expressions of α_{1A}- and α_{1B}-AR mRNAs in bladder mucosa from two groups (group 1: FDV ≤200 mL and/or SDV ≤ 300 mL; group 2: FDV ≥ 201 mL and/or SDV ≥ 301 mL) revealed no significant differences between the groups with respect to α_{1A}- and α_{1B}-AR mRNA levels. However, mucosa from the first group of patients had significantly more α_{1D}-AR mRNA than did that from the latter group of patients. There seem to be many molecular causes of storage symptoms,[29-32] not all necessarily involving urothelial α_1-ARs. Nevertheless, the finding of a relationship between urodynamic sensory parameters and the expression levels of urothelial α_1-AR mRNAs suggests that α_{1D}-ARs may play an important role in

storage symptoms in male LUTS patients.

2.3. What is the role of the α_{1D}-ARs in the human bladder?

Since the nonselective α_1-AR antagonist terazosin relieves nocturia, as assessed by frequency volume charts (FVCs),[33] one (or more) α_1-AR subtypes must be responsible for this effect. Both tamsulosin, which is an $\alpha_{1A/1D}$-AR selective antagonist (rather α_{1A}-AR selective), and naftopidil, which is an $\alpha_{1D/1A}$-AR selective antagonist (rather α_{1D}-AR selective), reduce the nocturnal frequency in FVC by decreasing nocturnal urine volume.[34,35] By contrast, silodosin, which is an α_{1A}-AR highly selective antagonist, does not decrease the number of nighttime voidings in FVC.[36] Then, is there evidence for α_{1D}-AR-related LUTS that was obtained by comparing the effects of a rather α_{1A}-AR selective antagonist and a rather α_{1D}-AR selective antagonist on bladder storage function? Nishino et al. reported interesting evidence from a PFS by comparing the two drugs in a randomized, cross-over design.[37] This study was conducted with an average prostate size of 20 mL in patients with severe symptoms (total IPSS ≥ 20). Tamsulosin and naftopidil caused no significant difference in voiding symptoms or total IPSS, but relief of storage symptoms, especially nocturia, was significantly greater with naftopidil. In PFS, moreover, the increases in the maximum desired volume and the first desired volume were higher with naftopidil than with tamsulosin. In 7 subjects who showed disappearance of involuntary contractions, disappearances were found in 5 subjects in each

cross-over period. In one subject, however, involuntary contractions disappeared during the first naftopidil period, but they returned after the switch to tamsulosin. In another subject, the cross-over to naftopidil resulted in disappearance of involuntary contractions, although the contractions continued with tamsulosin. In addition, both drugs decreased BOO grade. Kakizaki et al. have also investigated detrusor overactivity using a filling cystometry procedure in BPH patients with total IPSS storage symptom scores (frequency, urgency, and nocturia) ≥ 7.[38] In nine patients who had detrusor overactivity before naftopidil treatment, filling cystometry was repeated after treatment. Bladder volume at first desire to void increased significantly from 174 ± 92 mL to 259 ± 109 mL. These investigations support the suggestion that α_{1D}-AR may play an important role, at least in part, in sensory afferent nerve activity.

2.4. α_{1A}- or α_{1D}-AR subtype dominant in patients with BPH

Initial studies examining the α_1-AR subtype in human prostate using RNase protection assays and *in situ* hybridization approaches revealed that α_{1A}-AR predominates at the RNA level.[39] However, recent evidence demonstrated that, in addition to α_{1A}-AR, the α_{1D}-AR subtype was also present to a significant extent in human prostate using the real time RT-PCR procedure.[40] This study demonstrated that the median expression levels (interquartile range) of α_{1A}-AR and α_{1D}-AR were 1.25 (0.66-2.45) and 1.18 (0.71-2.27) × 1,000 copies/β-actin, respectively, with no significant

difference. Furthermore, the ratio of the mean expression level of each subtype to total α_1-AR was 41.2% and 49.1% for α_{1A}- and α_{1D}-AR mRNAs, respectively. The correlation between the expression of α_1-AR subtype mRNA in the prostate and the clinical efficacy of subtype-selective α_1-AR antagonists was also examined.[41] Patients who did not have malignant tumors based on prostate biopsy results were divided into two groups and given either tamsulosin or naftopidil. The efficacy of tamsulosin and naftopidil differed depending on the dominant α_1-AR subtype in the prostate. Tamsulosin was more effective in patients with dominant expression of the α_{1A}-AR subtype, whereas naftopidil was more effective in those with dominant expression of the α_{1D}-AR subtype. Although this theory may not be clinically applicable for all BPH patients because of the inconvenience of biopsy, the α_1-AR subtype mRNA expression level in the prostate could be a predictor of the efficacy of subtype selective α_1-AR antagonists. Genetic differences may be responsible for the diverse responses to these drugs.

3. SUMMARY

There is evidence that targeting only α_{1A}-AR may not provide comprehensive therapy for LUTS associated with BPH/BPO. The presence of α_{1D}-ARs in the lower urinary tract suggests that this subtype may play an important role in the pathophysiology of male LUTS.

Conflict of interest

None declared.

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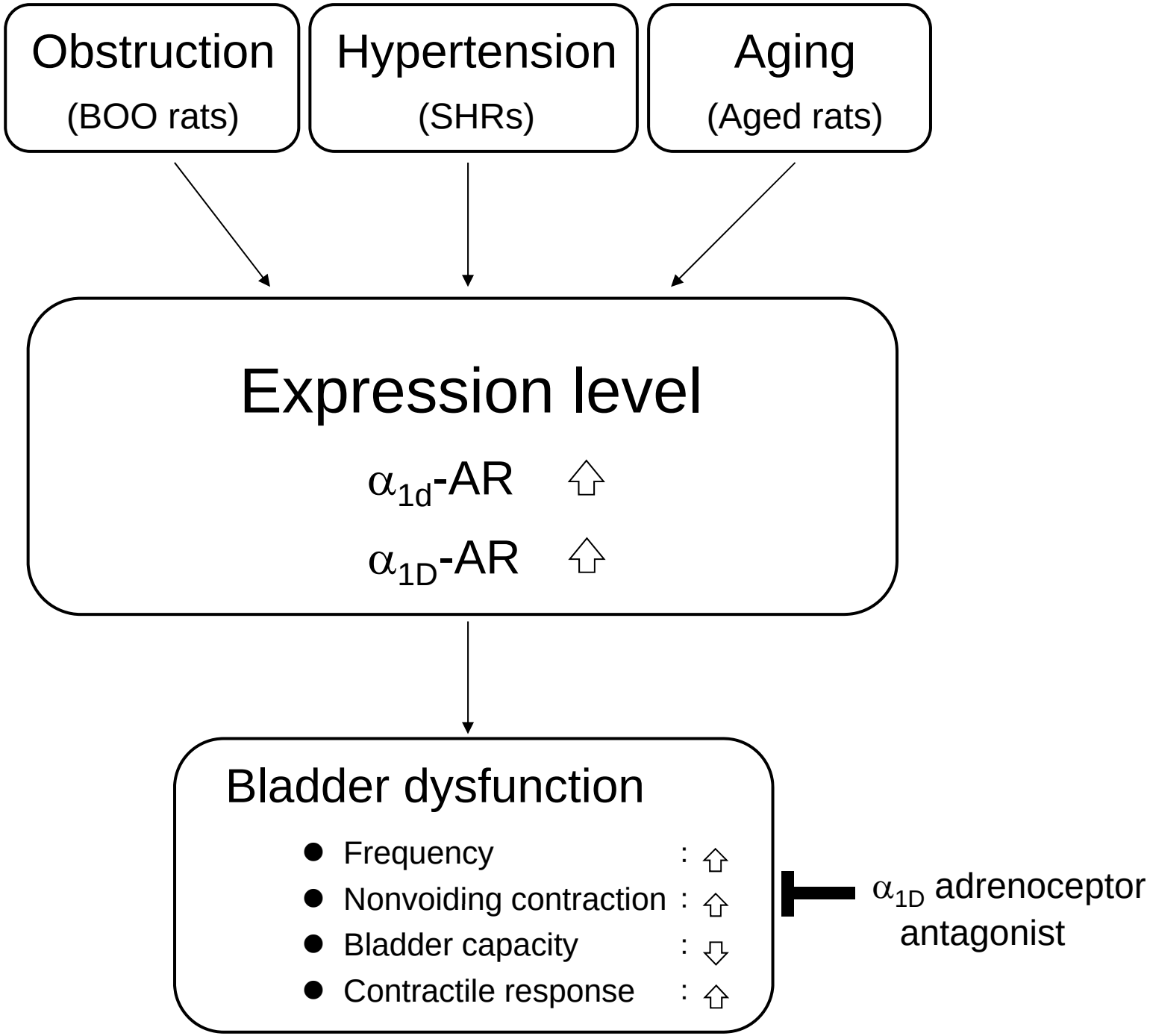
Legend of the figure

Fig.1

The expression level of α_{1D}-adrenoceptor (AR) mRNA or α_{1D}-AR protein increases by bladder outlet obstruction, hypertension and/or aging. This may be related to the male lower urinary symptoms, and α_{1D}-AR may become the target of the therapy.

Fig. 1


Obstruction
(BOO rats)
Hypertension
(SHRs)
Aging
(Aged rats)
Expression level
α_{1d}-AR ⇧
α_{1D}-AR ⇧
Bladder dysfunction
Frequency : ⇧
Nonvoiding contraction : ⇧
Bladder capacity : ⇩
Contractile response : ⇧
α_{1D} adrenoceptor antagonist