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Clinical implications from studies of α1 adrenergic receptor knockout mice

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ARTICLE INFO

Article history:
Received 31 August 2006
Accepted 2 November 2006

Keywords:
α1-Adrenergic receptors
Knockout mice
Lower urinary tract
Central nervous system
Drug development
Clinical implications

ABSTRACT

α1-Adrenergic receptors (α1-ARs) modulate a large number of physiological functions in cardiovascular and noncardiovascular tissues. Because individual members of the α1-AR family (α1A-, α1B-, and α1D-ARs) have overlapping expression profiles in most tissues, elucidation of the precise physiological roles of individual α1-AR subtypes remains a challenging task. To alleviate this constraint, a gene targeting approach has been employed to generate mutant mice lacking one or two α1-AR genes. Recent studies on these mutant mouse strains are discussed in this article, with an emphasis on the role of α1-AR in the central nervous system and lower urinary tracts. These are two major tissues of particular interest for the development of new therapeutic strategies targeted to the α1-ARs. By combining gene targeting techniques with pharmacological tools, the specific roles of α1-AR subtypes could be delineated.

1. Introduction

Three distinct subtypes of α1-adrenergic receptors (α1A-, α1B-, or α1D-ARs) belong to the superfamily of G protein-coupled receptors, which have seven putative transmembrane domains. The α1-ARs activate a Gq-mediated intracellular signaling pathway, while the other members of ARs, β-ARs and α2-ARs, are preferentially coupled to G proteins of the Gs and Gi classes, respectively [1,2]. The three α1-AR subtypes differ in terms of their subcellular distributions [3], their efficacy in evoking intracellular signaling cascades [4–7] and their transcriptional profiles [8]. Although a large body of knowledge has accumulated on cloned and artificially expressed α1-ARs obtained from diverse mammalian and non-mammalian species [9], correlations between receptor functions *in vivo* and specific characteristics of cloned α1-AR have been hampered due to a lack of pharmacological tools having sufficient specificity for each subtype, and due to frequent co-expression of two or three receptor subtypes in the same tissue preparation or even in the same cell [10]. When distinct α1-AR subtypes are co-expressed, it has been proposed that they can form hetero-, as well as homo-oligomeric α1-ARs [11]. Catecholamines, which are common agonists for all three α1-ARs, evoke intracellular signal transduction networks and mutual interactions among α1-AR subtypes. These interactions occur at the receptor level, as well as among intracellular signaling molecules.

To overcome complexities encountered in *in vivo* experiments and to elucidate subtype-specific functions, mice with altered α1-AR expression have been generated [12–17]. Mice with a deletion (knockout, KO) of one or two distinct α1-AR subtypes, or mice engineered to overexpress α1-AR (transgenic,

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Abbreviations: α1-ARs, α1-adrenergic receptors; KO, knockout; TG, transgenic; LUT, lower urinary tract; CNS, central nervous system; BPH, benign prostatic hypertrophy; WT, wild-type

0006-2952/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2006.11.002

TG) by using general or tissue specific promoters provide opportunities to characterize specific receptor(s) *in vivo*. The main focus of the article that we are contributing to this memorial issue is on the findings from α1-AR KO and α1-AR TG mice, which have shed light on the roles of α1-AR in the lower urinary tract (LUT) and the central nervous system (CNS). Owing to limitations of space, this article is not a comprehensive overview of the subject. For discussions concerning the variety of cardiovascular physiological roles of α1-AR and their implications for drug development, another recent review should also be consulted [18–23].

2. The role of α1-AR in LUT

Activation of α1-AR promotes closure of the bladder outlet. Thus, the α1-agonists have been considered to facilitate urine storage, and α1-AR antagonists have been used to facilitate voiding [24,25]. In patients with benign prostatic hypertrophy (BPH), stimulation of prostatic/urethral α1-AR contributes to the increased outlet resistance, and α1-AR-blocking agents have been useful in promoting bladder emptying and reducing symptoms as a component of conservative medical therapy [26].

Although all three α1-AR subtypes are present in the LUT and its nervous system [26,27], excessive activity of the α1A- and α1D-AR subtypes appears to be a common feature in symptomatic BPH [28]. Doxazosin, a non-selective antagonist, and tamsulosin, which has a high affinity for α1A- and α1D-AR subtypes relative to α1B-AR, showed similar clinical efficacy [28]. Human detrusor contains two α1-AR subtypes, α1D- and α1A-ARs, and the α1D-AR dominates over α1A-AR. However, a species difference was noted between rat and human detrusor muscles [29]. In the rat bladder, α1A-AR mRNA was predominant in the control condition [30]. Competition analysis using the α1D-AR selective antagonist BMY7378 revealed that the control rat bladder contains exclusively low affinity BMY7378 binding, while 6 weeks after outlet obstruction and bladder hypertrophy, the α1A-AR binding sites decreased and a new onset of α1D-AR expression occurred [30].

Besides urinary smooth muscle, α1-ARs are also present in the urothelium, where stimulation evokes the release of NO [31]. In rat bladder urothelium, α1D-AR appears to facilitate the mechanosensitive bladder nerve afferent activity and the micturition reflex [32]. α1-ARs are also found at various sites in the nervous system, including parasympathetic nerve terminals in the bladder [31,33,34]. Subtype-dependent roles are known on α1-ARs; α1A-AR mediates an enhancement of acetylcholine release, whereas α1B- and α1D-ARs mediate the direct excitatory effect on the bladder smooth muscle [31,33,34]. It is obvious that α1-ARs may also mediate effects in other locations important for LUT symptom generation, including the smooth muscle, the detrusor vasculature, afferent and efferent nerve terminals, and intramural ganglia. In addition, α1-ARs within the peripheral and CNS (spinal and/or supraspinal) appear to be important for bladder function.

At the spinal level, norepinephrine derived from the locus coeruleus was shown to activate preganglionic neurons in the sacral intermediolateral nuclei via α1-ARs, thereby producing urinary bladder contraction [35]. Intrathecal injection of doxazosin suppressed the amplitude of reflex bladder contractions in anaesthetized rats, while it increased the frequency of isovolumetric contractions, indicating the presence of a tonic adrenergic inhibitory mechanism [34]. Therefore, current thought suggests that α1-blockers work partly on the CNS [36].

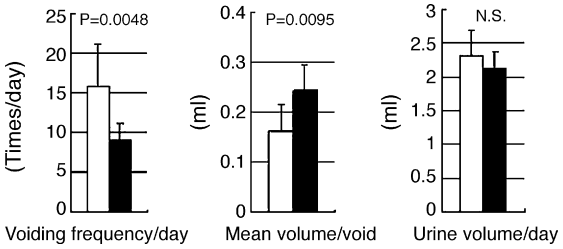

Fig. 1 – Results of 48-h frequency/volume analysis of α1D-KO mice. Daily voiding frequency was significantly lower in α1D-KO vs. WT mice (9.0 ± 2.1 vs. 15.9 ± 5.2 times, $p = 0.0012$). Mean urine volume per void was significantly larger in α1D-KO vs. WT mice (0.24 ± 0.02 vs. 0.16 ± 0.03 ml, $p = 0.0024$). No significant differences were observed in daily total urine volume between the two groups. N.S., not significant. This figure is reproduced from [39] with permission.

It was found by intrathecal injection that both tamsulosin and naftopidil transiently abolished isovolumetric rhythmic bladder contractions, and that the effects were reversible [37]. The amplitude of bladder contraction was decreased by naftopidil, but not by tamsulosin. The authors suggested that both drugs blocked the afferent limb rather than the efferent limb of the micturition reflex pathway, and that the main α1-AR in the afferent limb of this reflex pathway may be α1D-AR [37]. In the human spinal cord, all three α1-AR subtypes were found to be present, and α1D-AR mRNA predominated overall [38].

To investigate the effect of deleting the α1D-AR gene, Chen et al. investigated the LUT functions in female α1D-AR KO mice using frequency/volume analysis and filling cystometry [39]. In the bladder of wild-type (WT) mice, mRNA for α1A- and α1D-ARs were found with minimal expression of the α1B-AR subtype. In α1D-KO mice the amount of α1A- and α1B-AR in the bladder was similar to that in WT mice. Using a metabolic cage, mean daily voiding frequency of awake and unrestrained α1D-KO mice was found to be significantly lower than in WT mice (Fig. 1). Mean volume per void in α1D-KO mice was significantly larger than in WT mice (Fig. 1). In line with the results from voiding frequency/volume measurements, cystometric analysis of freely moving mice demonstrated that α1D-KO mice had a larger bladder capacity and voided volume compared with WT mice. No significant difference in maximum pressure at void was observed between the two groups (Table 1).

The results from α1D-KO mice clearly demonstrate that the α1D-AR subtype has an important role in regulating bladder function. They also theoretically support a clinical finding that α1-blockers with significant affinity for α1D-AR are effective for treating storage symptoms associated with benign prostatic

Table 1 – Cystometric results in WT and knockout mice

	WT (mean ± S.D.)	α1D-KO (mean ± S.D.)	*p*-Value
Bladder capacity (ml)	0.15 ± 0.01	0.21 ± 0.01	0.0008
Voided volume (ml)	0.13 ± 0.01	0.19 ± 0.02	0.0048
Residual volume (ml)	0.02 ± 0.01	0.02 ± 0.01	Not significant
Maximum void pressure (mm Hg)	34.9 ± 1.6	33.5 ± 1.5	Not significant

This table is reproduced from Ref. [39] with permission from the American Urological Association.

obstruction. The future study on α1D-KO mice should address the location of the α1D-AR involved in micturition control [40].

3. α1-ARs in the central nervous system

All three α1-AR subtypes are expressed throughout the CNS. High levels of α1A-AR mRNA were found in the olfactory system, in several hypothalamic nuclei, and in regions of the brainstem and spinal cord, particularly in areas related to motor function [41]. Expression of α1B-AR was abundant in the pineal gland, thalamic nuclei, the lateral nucleus of the amygdala, the intermediate and deep layers of the cortex, and in the dorsal and median raphe nuclei [41–43]. A study using α1B-AR KO mice showed that [^{3}H]-prazosin binding densities were dramatically decreased in layer III of the cerebral cortex and in the thalamus [44]. The distribution of α1D-AR was the most discrete among these receptors. It was strongly expressed in the olfactory bulb, the reticular thalamic nucleus, the hippocampus and layers II–V of the cerebral cortex containing the thalamic inputs, regions of the amygdala, the motor nuclei of the brainstem and in the spinal cord [41–43]. Analysis of mice having targeted displacement of α1D-AR to LacZ gene revealed that β-galactosidase activities were found in the cortex, hippocampus, olfactory bulb, dorsal geniculate and ventral posterolateral nuclei of the thalamus [45].

Studies on mutant mice suggest that α1-AR especially α1B- and α1D-AR subtypes, appear to be involved in CNS processes such as responses to psycostimulants, nociceptive responses, locomotor activity, modulation of memory consolidation and working memory (see below).

4. Behavioral changes in α1B-AR KO

Psychostimulants such as amphetamine and cocaine, as well as opiates cause drug addiction in humans and induce locomotor stimulant effects in rodents [46]. After a single administration of these drugs, rodents generally increase their spontaneous locomotor activity. After repeated intermittent injections of the psychostimulants, locomotor responses are enhanced and behavioral sensitization becomes evident. Thus, repeated treatments with *d*-amphetamine, cocaine, or morphine lead to a progressive increase in the locomotor responses of WT animals that is correlated with the number of drug administrations.

In contrast to WT mice, induction of the locomotor hyperactivity and behavioral sensitization by *d*-amphetamine, cocaine, or morphine were dramatically decreased in mice lacking the gene for α1B-AR [44]. Rewarding properties could not be observed in KO mice, which were subjected to an oral preference test using cocaine and morphine, and a conditioned place preference using morphine. Basal dopaminergic transmission as well as locomotor activity after administration of D1 dopamine receptor agonist were similar in α1B-AR KO and WT mice, ruling out a congenital deficit in the dopaminergic system of KO mice [44]. In line with these behavioral changes, basal and *d*-amphetamine-stimulated extracellular DA levels in the nucleus accumbens were lower in α1B-AR KO than in WT littermates [47].

The α1B-AR KO mice, on the other hand, exhibit an increased response to a serotonin releaser, *p*-chloroamphetamine, when administered to the prefrontal cortex and they show locomotor hyperactivity. This result indicates interactions between noradrenergic and serotonergic neurons in the formation of psychostimulant-induced locomotor responses [48]. Indeed, in the mice lacking the 5-HT$_{2A}$ serotonin receptor, *d*-amphetamine increased their locomotor activity and cortical norepinephrine release [48].

Analysis of higher order CNS functions indicated that the α1B-AR KO mice showed significantly reduced square entries and a reduced rearing behavior in the open field test. In passive avoidance procedures, α1B-AR KO showed a tendency towards decreased short-term-latency and a significant decline in long-term-latency [49]. Thus, the authors concluded that α1B-AR is possibly involved in modulation of memory consolidation and fear-motivated exploratory activity. It was also pointed out that these KO mice may be useful for studying dementia. The α1B-AR KO was also reported to show impaired spatial learning in the water maze but an increased reaction to novelty [50].

5. CNS functions of α1D-AR KO

When the ability to sense nociceptive stimuli was assessed in mutant mice lacking α1D-AR, the mice showed longer tail-flick and hindpaw-licking latencies, suggesting that α1D-AR KO mice are relatively insensitive to noxious heat stimuli compared to the WT [51]. Since expression of α1D-AR mRNA was found in the spinal cord at the dorsal and ventral horn, spinal α1-AR was considered, at least in part, to participate in the spinal reflex induced by the noxious thermal stimuli. In contrast to the hindpaw-licking, the jumping latency in the hot plate test was shorter. The jumping response appears to have a more emotional component, and α1D-AR mRNA was detected in limbic structures such as the hippocampus, the cingulate cortex and the amygdala. Therefore, escape behavior in response to noxious stimuli might be affected in α1D-AR KO mice [51].

The behavioral study demonstrated that α1D-AR KO mice showed better motor coordination at the highest rotating speed of the rotarod test and stronger muscle tone when assessed with the traction meter [52]. In the water maze test requiring reference memory, α1D-AR KO mice showed normal spatial learning, while in the Y-maze task requiring working memory or attention, these KO mice displayed an impaired spontaneous alternation performance [52]. The α1D-AR KO mice tended to display lower levels of acoustic startle responses than did the WT group at lower pulse intensities, although the acoustic pre-pulse inhibition was not impaired. Furthermore, the effect of the NMDA receptor antagonist, MK-801, which usually suppresses pre-pulse inhibition, was not obvious. These results suggest that basal activity of the NMDA receptor system leading to acoustic pre-pulse inhibition might be reduced [52]. The α1D-AR plays an important role in the processes of auditory sensory function, attention or working memory rather than reference memory, and in the sensorimotor gating deficits induced by the NMDA receptor antagonist [52].

Wheel-running activity of α1D-AR KO is significantly reduced during the subjective night, or in the active phase. Furthermore, exploratory rearing behavior in a novel cage environment was significantly reduced in these mice. Acute amphetamine administration to α1D-AR KO mice resulted in reduced hyperlocomotion, suggesting the functional importance of α1D-AR in mediating a variety of stimulus-induced changes in locomotor behaviors [45].

6. CNS functions of transgenic mice expressing α1B-AR

Overexpression of the wild type and of the constitutively active forms of α1B-AR under intrinsic promoter activity provided a unique opportunity to study CNS functions of α1B-AR including age-progressive impaired mobility, neurodegeneration and susceptibility to epileptic seizure [14]. To investigate the molecular basis of this phenotype, oligonucleotide microarray studies of whole brains of various ages were performed [53]. The results indicated differential expression between WT and KO mice of genes for regulating apoptosis, calcium signaling, neurodegeneration and neurotransmission. An observed increase in the expression of NMDA receptors (stimulatory), and decreased $GABA_A$ receptors (inhibitory) in transgenic murine brains could provide a potential molecular basis for neurodegeneration induced by overexpressed, constitutively active α1B-AR [53].

7. Concluding remarks

The advantages of using mice to study α1-ARs reside in the availability of powerful technology to modify gene expression *in vivo*. Several complicating factors, however, should be kept in mind when interpreting the results from mutant mice experiments. The up- or down-regulation of another component of a signaling pathway could compensate the loss of a functional receptor in a genetically engineered mouse. In fact, hepatocytes from α1B-AR KO mice reveal compensatory adrenoceptor subtype substitution [54]. To avoid any compensatory adaptations that might occur during development, it would be valuable to have mice with inducible gene KOs, as they would more closely resemble acute blockade of specific α1-AR subtypes. In studying behavior, environmental factors can have a large influence on the phenotype. Different behavioral phenotypes were found by different laboratories using the same mouse strains, and different phenotypes were even recorded in the same laboratory at different times [55]. Thus, reproducibility and proper controls are crucial for establishing confidence in the behavioral consequences of modifying gene expression.

An RNA-based knock down strategy using antisense or short interference RNA could be an alternative method to delete a specific α1-AR gene. An antisense study by Hrometz et al. revealed that renal artery contraction was induced by the α1A-AR-selective agonist A-61603 and was specifically reduced by *in vivo* application of antisense oligonucleotides targeted against the α1A-AR found in the renal artery [56].

In conclusion, both genetically altered model animals and pharmacological tools are helping to improve our knowledge of the subtype-specific roles of α1-ARs *in vivo*. By understanding precise spatio-temporal regulation of α1-AR function, a better strategy for drug development directed to α1-AR, and pitfalls of α1-AR blockage will eventually be delineated.

Conflict of interest

Authors disclose no conflict of interest.

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