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REVIEW

Similarities and differences in the autonomic control of airway and urinary bladder smooth muscle

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Abstract The airways and the urinary bladder are both hollow organs serving very different functions, i.e. air flow and urine storage, respectively. While the autonomic nervous system seems to play only a minor if any role in the physiological regulation of airway tone during normal breathing, it is important in the physiological regulation of bladder smooth muscle contraction and relaxation. While both tissues share a greater expression of M_2 than of M_3 muscarinic receptors, smooth muscle contraction in both is largely mediated by the smaller M_3 population apparently involving phospholipase C activation to only a minor if any extent. While smooth muscle in both tissues can be relaxed by β-adrenoceptor stimulation, this primarily involves β_2-adrenoceptors in human airways and β_3-adrenoceptors in human bladder. Despite activation of adenylyl cyclase by either subtype, cyclic adenosine monophosphate plays only a minor role in bladder relaxation by β-agonists; an important but not exclusive function is known in airway relaxation. While airway β_2-adrenoceptors are sensitive to agonist-induced desensitization, β_3-adrenoceptors are generally considered to exhibit much less if any sensitivity to desensitization. Gene polymorphisms exist in the genes of both β_2- and β_3-adrenoceptors. Despite being not fully conclusive, the available data suggest some role of β_2-adrenoceptor polymorphisms in airway function and its treatment by receptor agonists, whereas the available data on β_3-adrenoceptor polymorphisms and bladder function are too limited to allow robust interpretation. We conclude that the distinct functions of airways and urinary bladder are reflected in a differential regulation by the autonomic nervous system. Studying these differences may be informative for a better understanding of each tissue.

Keywords Airway · Urinary bladder · Muscarinic receptor · β_2-adrenoceptor · β_3-adrenoceptor

The airways and the urinary bladder are hollow organs. Their walls contain smooth muscle which allows for contraction and relaxation. The inner surface of both is covered by an epithelial layer, which is termed urothelium in the bladder and respiratory epithelium in the airways. The function of both organs is primarily regulated by the autonomic nervous system, but bladder contraction to a certain degree is under voluntary control. However, the airways and the bladder serve very different purposes within the mammalian body. While the airways are filled with air and primarily serve the purpose of air flow to ultimately yield gas exchange, the bladder is filled with urine and allows for only limited absorption and secretion (Krege et al. 2004). While the airways undergo several filling/emptying cycles every minute, only one such cycle occurs in a healthy human bladder every couple of hours. This article will explore how the autonomic control of smooth muscle function differs between the airways and the bladder. A general summary of key features is presented in Table 1.

The authors wish to dedicate this manuscript to Prof. Hans Zaagsma on the occasion of his retirement.

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Table 1 Summary of similarities and differences in autonomic control of airway and bladder smooth muscle

Feature	Airways	Bladder
Filling	Passive	Passive
Changes in volume	<2 times	>10 times
Emptying	Passive	Active
Filling/emptying cycles (per hour)	Frequent	Sporadic
Autonomic receptor mediating relaxation	β_2-adrenoceptor	β_3-adrenoceptor
Relaxing signalling	cAMP, BK_{Ca}	BK_{Ca}
Autonomic receptor mediating contraction	M_3-muscarinic	M_3-muscarinic
Contracting signalling	Phospholipase C-β, cyclic ADP-ribose, rho kinase	Voltage-operated Ca channels, rho kinase
Cholinergic prejunctional feedback	Important M_2-muscarinic inhibition	M_2- and M_4-muscarinic inhibition and M_1 facilitation

Physiological considerations

Filling of both the airways and the bladder is primarily driven by forces outside the tissue. In the case of the airways, filling during inhalation occurs largely passively as a result of the contraction of striated muscles such as the diaphragm which increases intrathoracic volume. The relaxation of airway smooth muscle serves only a modulating role in accommodating the air, as it is used to lower airway resistance under conditions of physical or emotional stress when the organisms needs extra oxygen. Thus, even a maximum relaxation of airway smooth muscle increases airway volume by much less than 100%. This airway smooth muscle relaxation is mediated by β-adrenoceptors, largely belonging to the β_2 subtype in several mammalian species including humans (Mak et al. 1996). The bladder filling is also largely driven passively as it occurs secondary to the urine output by the kidneys. However, the relaxation of bladder smooth muscle plays a crucial role in this process as it allows accommodating increasing volumes of urine without major increases in intravesical pressure (Andersson 1993). Considering that the physiological amount of urine in the bladder at the start of each micturition cycle is less than 50 ml and that a healthy bladder can easily hold 500 ml of urine, the bladder must accommodate greater than tenfold changes in volume and hence have an enormous compliance. This compliance is mainly mediated by β-adrenoceptor-driven bladder smooth muscle relaxation, which in most mammalian species including humans predominantly occurs via the β_3 subtype (Michel and Vrydag 2006).

Emptying of the lung is largely driven by its elastic properties. The autonomic nervous system does not play a major role in narrowing airway diameter during physiological breathing; however, it can cause major airway contraction as a defense against inhaled toxic substances or during pathophysiological conditions. Paradoxically, instead of improving emptying, parasympathetically evoked bronchial smooth muscle contraction impairs it by increasing airway resistance. Such contraction is mediated by muscarinic acetylcholine receptors of the M_3 subtype (Fisher et al. 2004). In contrast, the physiological emptying of the urinary bladder is largely mediated by bladder smooth muscle contraction. Nevertheless, this process is also driven by muscarinic receptors of the M_3 subtype (Hegde 2006). While bladder emptying is driven by smooth muscle contraction in the detrusor, it is accompanied by muscle relaxation of the urethra to allow an undisturbed flow of urine. However, the autonomic control of the urethra will not be discussed here. Interestingly, the major difference in the length of a filling/emptying cycle between airways and bladder (seconds vs. hours) is largely due to differences in the length of the filling phase, whereas the emptying phase occurs almost equally quickly in both tissues. It is tempting to speculate that the differential role of β_2- vs. β_3-adrenoceptors in relaxation as compared to the similar role of M_3 receptors in contraction may relate to these differences in the duration of filling. The following will discuss in more detail similarities and differences in the regulation of airway and bladder smooth muscle contraction and relaxation by muscarinic receptors and β-adrenoceptors, respectively.

Parasympathetic control of smooth muscle contraction

While the parasympathetic innervation of the airways is provided by the vagus nerve, that of the bladder comes from the pelvic nerves originating in the sacral spinal cord. However, in both tissues the acetylcholine may also come from non-neuronal sources (see below). Smooth muscle from both tissues expresses mainly the M_2 and the M_3 subtype of muscarinic receptors, and in many species the M_2 subtype is expressed more prominently than the M_3 subtype at both the mRNA and the protein level (Coulson and Fryer 2003; Goepel et al. 1998; Roffel et al. 1988). Nevertheless, smooth muscle contraction of the airways (Coulson and Fryer 2003; Roffel et al. 1990, 1988) and the bladder (Abrams et al. 2006; Hegde 2006) occurs largely if not exclusively by M_3 receptors. Accordingly, isolated airway tissue from M_2 receptor knock-out mice shows only modest impairment of muscarinic agonist-induced contraction (Stengel et al. 2000; Struckmann et al. 2003) or bladder contractility (Igawa et al. 2004), whereas M_3 receptor

knock-out mice exhibit major impairments in both tissues (Fisher et al. 2004; Igawa et al. 2004; Matsui et al. 2000; Stengel et al. 2002; Struckmann et al. 2003). Accordingly, antagonists which preferentially inhibit M_3 receptors such as tiotropium (Disse et al. 1999; Koumis and Samuel 2005) in the airways and darifenacin (Croom and Keating 2004; Maruyama et al. 2006) and solifenacin (Armstrong et al. 2008; Chapple 2006; Oki et al. 2005) in the bladder appear to have similar therapeutic efficacy as non-selective muscarinic antagonists, further supporting the major role of M_3 receptors in regulating contraction in both tissues. However, in both airways and bladder M_2 receptors may have a physiological role in opposing smooth muscle relaxation mediated by β-adrenoceptors during the filling phase (Ehlert et al. 2007; Matsui et al. 2003; Sarria et al. 2002). Moreover, at least in airways, prejunctional inhibitory M_2 receptors play a major role in regulating smooth muscle tone (Coulson and Fryer 2003). While prejunctional muscarinic receptors also exist in the bladder, they appear to play a smaller functional role in the regulation of smooth muscle tone than those in the airways. Nevertheless, prejunctional inhibitory M_2-receptors also exist in the bladder (Trendelenburg et al. 2003) but additional inhibitory M_4-receptors (D'Agostino et al. 1997, 2000) and facilitatory M_1-receptors also exist (Somogyi et al. 1996).

A stimulation of phospholipase C (PLC) with the subsequent formation of inositoltrisphosphate and diacylglycerol is the prototypical signalling pathway of M_3 receptors. This can also be shown in airways (An and Hai 1999) and bladder (Kories et al. 2003) using subtype-selective antagonists, and studies with knock-out mice confirm such observations (Tran et al. 2006). Nevertheless, PLC does not appear to contribute to bladder contraction by muscarinic agonists in a major way. This was first proposed based upon the PLC inhibitor U 73,122 in rat (Schneider et al. 2004b), mouse (Wegener et al. 2004) and human bladder (Schneider et al. 2004a); in those studies U 73,122 did not affect bladder contraction in concentrations where it fully suppressed inositol phosphate formation (Schneider et al. 2004b). However, using different experimental designs and different PLC inhibitors other investigators have proposed a role for PLC in bladder contraction (Braverman et al. 2006a, b). In a subsequent collaborative study between the groups reporting evidence in favor and against a role for PLC in bladder contraction, it was found that previously shown differences relate to the choice of PLC inhibitor rather than experimental conditions; more importantly, the overall evidence did not support a major role of PLC in bladder contraction (Frazier et al. 2007). Thus, despite a prominent role for PLC in M_3 receptor function, other signalling pathways apparently carry M_3 muscarinic receptor-mediated contraction bladder contraction (Frazier et al. 2008). Interestingly, some muscarinic receptor antagonists such as propiverine and its metabolites also have direct effects on Ca^2 influx, which may contribute to their clinical effects (Wuest et al. 2006, 2007). While we are not aware of similar systematic studies in the airways, it has been shown that Ca^2 oscillations in the airways do not necessarily require PLC activation (Sney et al. 2003). Similar to the bladder, other signalling pathways including cyclic ADP-ribose and Rho-kinase may be relevant for muscarinic receptor-mediated airway contraction (Deshpande et al. 2005; Lutz et al. 2005).

While the classical view dictated that formation of neurotransmitters is an exclusive property of neurons, it has meanwhile become clear that non-neuronal acetylcholine formation exists in several tissues. Major parts of the evidence in this regard come from the airways, the intestine, the skin, and the urinary bladder. Thus, the urothelium expresses the enzymes required for acetylcholine synthesis and forms acetylcholine (Lips et al. 2007). Urothelium-derived acetylcholine may act on muscarinic receptors within the urothelium including those on afferent sensory nerves as well as those on bladder smooth muscle (Bschleipfer et al. 2007; Zarghooni et al. 2007). Airways smooth muscle, goblet, basal, mast, and ciliated cells also express choline acetyl transferase and/or produce acetylcholine, and this has been proposed to be a potential target of drug treatment (Wessler and Kirkpatrick 2001).

Sympathetic control of smooth muscle relaxation

While all three classes of adrenoceptors are expressed in both airways and bladder, postjunctional α_1- and α_2-adrenoceptors do not contribute to the regulation of smooth muscle tone in either tissue in a major way (Goldie et al. 1990; Michel and Vrydag 2006). While β-adrenoceptors are abundantly expressed in both tissues, they mostly belong to the β_2-subtype in the airways of many mammalian species including humans (Goldie et al. 1990). The expression pattern of β-adrenoceptor subtypes in the bladder is less clear. In humans, the β_3-subtype appears to be by far the most prominently expressed subtype at the mRNA level (Nomiya and Yamaguchi 2003; Otsuka et al. 2008). Quantitative data on mRNA expression of β-adrenoceptor subtypes in other species are not available. Data on protein expression of β-adrenoceptor subtype expression in the bladder are not conclusive as no validated antibodies or suitable radioligands exist (Niclauß et al. 2006; Vrydag and Michel 2007).

Functional studies demonstrate very clearly that the β-adrenoceptor-mediating airway smooth muscle relaxation belongs predominantly if not exclusively to the β_2-subtype (Goldie et al. 1990) although in some species, e.g. guinea pigs, β_1-adrenoceptors may contribute (Tanaka et al. 2007). In most species β_3-adrenoceptors make a substantial

contribution to bladder relaxation and may be the only subtype of functional relevance in the human bladder (Michel and Vrydag 2006). Thus, airways and bladder differ considerably with regard to the β-adrenoceptor subtypes being expressed and mediating smooth muscle relaxation.

The prototypical signalling pathway of β-adrenoceptors is a G_s-mediated coupling to an activation of adenylyl cyclase leading to the formation of cyclic adenosine monophosphate (cAMP). However, data from various cell types indicate that other signalling pathways may also be functionally relevant (Scherer et al. 2007) and, e.g. in vascular smooth muscle the activation of certain types of K channels is a major pathway involved in β-adrenoceptor-mediated relaxation (Bieger et al. 2006; Ferro 2006). Other signalling pathways such as cyclooxygenase (Kang et al. 2007) or NO synthase (Bieger et al. 2006) may also be involved. Against this background, several studies have evaluated the contribution of the cAMP/protein kinase A pathway relative to other signalling pathways in the β-adrenoceptor-mediated relaxation of airway and bladder smooth muscle. In the urinary bladder, two independent studies in rats demonstrate that cAMP formation plays only a minor if any role in smooth muscle relaxation whereas K channels, particularly of the BK_{Ca} type may make major contributions (Frazier et al. 2005; Uchida et al. 2005). Similar studies in the airways of various species including humans (Miura et al. 1992) have also indicated major cAMP-independent components of relaxation responses to β-adrenoceptor stimulation, including the stimulation of BK_{Ca} channels (Giembycz and Newton 2006; Johnson 2006).

β_2-Adrenoceptors are known to undergo a rapid and profound agonist-induced desensitization which under chronic conditions involves down-regulation of the receptor (Tran et al. 2007). Accordingly, β_2-adrenoceptors in the lung have also been shown to undergo agonist-induced desensitization (Finney et al. 2001; Hauck et al. 1997; January et al. 1998). This may become therapeutically important during chronic treatment with β-adrenergic agonists, but its clinical importance remains controversial (Johnson 2006). In contrast, β_3-adrenoceptors lack the phosphorylation sites believed to be important in desensitization and are believed to be relatively resistant to agonist-induced desensitization (Carpene et al. 1993; Chaudhry and Granneman 1994). Preliminary data indicate that rat bladder β-adrenoceptors may undergo some agonist-induced desensitization but it remains to be determined if that affects the β_3-component of the response (Vrydag and Michel 2008). A possible rationale for this difference between airways and bladder may be rooted in the fact that the bladder β-adrenoceptors have to function during a filling phase of several hours, which would be hampered if they undergo rapid desensitization. However, detailed studies on the sensitivity of bladder β-adrenoceptors in response to prolonged agonist exposure have not been reported.

The regulation of lung and bladder β-adrenoceptors has also been studied during ageing and in pathophysiological settings. Airway β_2-adrenoceptor function may be reduced in aged animals (Fraeyman et al. 1993; Preuss et al. 1999), and a minor desensitization of bladder β-adrenoceptors has also been reported in aged rats (Michel and Barendrecht 2008). In contrast to e.g. cardiac β_1-adrenoceptors, the β_2-adrenoceptors in the lung do not exhibit down-regulation in spontaneously hypertensive rats but rather may even be up-regulated (Michel et al. 1987) and functionally have enhanced sensitivity to agonist stimulation (Kamibayashi and Ramanathan 1989). In contrast, β-adrenoceptors in the bladder of spontaneously hypertensive rats were reported to exhibit a minor desensitization (Frazier et al. 2006).

Within the bladder, β-adrenoceptors are not only expressed on smooth muscle cells but also on the urothelium (Harmon et al. 2005). Their stimulation may affect the ability of β-adrenoceptor agonists to induce bladder relaxation (Otsuka et al. 2008). Similarly, airway β-adrenoceptors are also not only found on smooth muscle but also on ciliated epithelial and mucus cells, where they can increase the beating frequency of the cilia and discharge of glycoprotein, respectively; moreover, β_2-adrenoceptors on lung mast cells may indirectly affect lung function by inhibiting the release of the bronchoconstrictor histamine (Johnson 2006; Johnson and Rennard 2001).

The genes of all three β-adrenoceptor subtypes are polymorphic (Leineweber et al. 2004). Studies with regard to pulmonary function have focused on polymorphisms in the amino acid positions 16 and 49 of the β_2-adrenoceptor and indicate that such polymorphisms may affect the speed of agonist-induced desensitization of airway smooth muscle cells (Moore et al. 2000) and also on lung mast cells (Chong et al. 2000; Kay et al. 2003). Whether this translates into clinically relevant effects on the prevalence of airways disease or its treatment by β-adrenoceptor agonists, remains controversial (Brodde and Leineweber 2005; Szalai et al. 2008; Thakkinstian et al. 2005). β_2-Adrenoceptor polymorphisms may also play a role as modifying-genes in diseases such as cystic fibrosis (Büscher and Grasemann 2006). With regard to β_3-adrenoceptor polymorphisms and bladder function, only a single study has been reported until now demonstrating that the Trp64Arg polymorphism is more frequently present in patients with overactive bladder syndrome than in those without (Honda et al. 2006).

β_2-Adrenoceptor agonists have long been used as bronchodilating drugs, whereas only very recently a single proof-of-concept study has demonstrated that a β_3-adreno-

ceptor agonist may alleviate bladder dysfunction in patients with overactive bladder (Chapple et al. 2008). However, the chronic use of β_2-adrenoceptor agonists in the treatment of airway disease has been questioned on safety grounds (Salpeter et al. 2006). In contrast, it has been reported that chronic (but not acute) administration of β-adrenoceptor antagonists may have beneficial effects in mouse models of asthma (Callaerts-Vegh et al. 2004; Nguyen et al. 2008). Therefore, in analogy to the situation in heart failure (Brodde 2007), it has been advocated that β-adrenoceptor antagonists may have some value in the chronic treatment of asthma (Bond et al. 2007). A clinical pilot study in asthma patients has been reported which supports such claims (Hanania et al. 2008). The relative benefits of agonist and antagonist treatment in airway and bladder disease certainly requires considerable additional study.

Conclusions

Based upon their differential functions, the morphology and autonomic control differs considerably between the airways and the urinary bladder. Nevertheless, a number of interesting similarities exist in the way the autonomic system controls the two tissues. Moreover, the differences in autonomic control may also be quite informative, particularly with regard to the relative role of β-adrenoceptor subtypes. Therefore, we propose that researchers interested in the autonomic control of either tissue may benefit from keeping an eye on the other tissue. While beyond the scope of this article, expanding the scope even further to other hollow organs including the gut and the heart (Brodde and Michel 1999) may provide additional comparative insight.

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