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Nitric Oxide and Ion Channels in Lower Urinary Tract

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Introduction

The storage and periodical release of urine are dependent on the activity of smooth and striated muscles of the urinary bladder, urethra and external urethral sphincter. It is essential for a normally functioning bladder that it is filled with urine at low pressures. Kidney filters the blood using relatively low glomerular capillary pressure. A back up pressure in the ureters by continued bladder pressure rise can stop filtration and damage the kidneys. To keep normal shape of the bladders during filling, a simultaneous contraction of the smooth muscle and a rapid increase in intravesical pressure empty the bladder. In addition, the smooth muscle cells must be able to constantly adjust their length in response to filling and this spontaneity is done through generation of action potential.

Smooth muscles of the urethra and bladder display characteristic patterns of spontaneous contractile activity in the filling phase of micturition cycle. Urethral smooth muscle shows phasic contractions. L-type Ca2+ channels maintain the smooth muscle tone which falls with Ca2+ channel blockers. Phasic contractions with frequencies that are species specific have been demonstrated in isolated detrusor strips [1].

Urinary symptoms of frequency and urgency are common with problem of bladder over activity. In absence of any pathological factors, bladder over activity may be with or without urge incontinence. Women are the worst sufferer than men in bladder over activity and its incidence increases with age. Its prevalence in adults is 16-17%.

Voiding dysfunction results either from failure to store urine, or from failure to empty. Storage problems arise due to anatomical defects in the urethral outlet, or over activity of the bladder from neurological disorders or from changes either in the brain or bladder during aging. On the other hand, urinary retention may occur due to obstruction of the urethral outlet (e.g. prostate enlargement), neural injury and /or diseases damaging nerve (e.g. diabetes mellitus) or drugs that depress the neural control of the bladder [2].

Ion Channels and Urethra

Extensive patch clamp experiments using various K+ channel blockers lead to the conclusion that three types of K+ channels viz. small and large Ca2+- activated K+ channels and KATP channels are present in the urethral myocytes. Continuous spontaneous tone generated by isolated strips is dependent on Ca2+ entry and is reduced by L-type Ca2+-channel blockers, NO donors and KATP openers [3].

The ability of L-type Ca2+ channel blockers to relax spontaneous tone shows that these channels are present in normal unstimulated pig strips. Both L- and T-type Ca2+ channels are present in rabbit and human urethral myocytes [4,5].

Ion Channels and Detrusor

K+ channels in the detrusor

The frequency of spontaneous action potentials and the probability of Ca2+ channel opening in bladder smooth muscle are voltage dependent. Therefore, to depress the contractility of bladder smooth muscle, membrane hyper polarization is an effective mechanism. Detrusor myocytes possess several types of K+ channel including large and small Ca2+-activated channels as well as voltage-sensitive K+ and KATP channels. Both K+ channel opening drugs (chromakalim, pinacidil and ZD 6169) and membrane hyper polarization inducing drugs are very effective suppressant of spontaneous action potentials and of contractions of isolated detrussor smooth muscle. Pinacidil and cromakalim have been reported to abolish spontaneous mechanical activity and unstable contractions in pig model [6,7]. Unfortunately, because they tend to reduce the blood pressure, KATP channel openers are not suitable for clinical use. New KATP channel openers, such as ZD6169, have been shown to be more selective for the bladder and oral administration reduces the voiding frequency but in rats and dogs without lowering blood pressure.

Calcium channels in the detrusor

L-type channels are important for mediating the upstroke of the action potentials, but T-type channels are also present in the detrusor. In response to large depolarization, L-type channels switch into a long channel open mode. In addition, activation of ryanodine receptors triggers release of Ca2+ from adjacent sarcoplasmic reticulum. Ca2+ can both inactivate the L-type channels as well as open Ca2+- activated K+ channels

[8], thus causing rapid depolarization and action potential after hyperpolarization. The effects of ryanodine on the spontaneous contractions depend on dose. In guinea pig 50μM of ryanodine can enhance the amplitude and reduce the frequency while with 10μM, there is a transient increase in the amplitude followed by a decrease in frequency with little change in the amplitude [9]. T-type channels, which might play a role in generating spontaneous activity are activated at more negative potentials.

Nitric Oxide and Lower Urinary Tract

Nitric oxide is now an important physiological cell mediator in the NANC neuronally mediated relaxation of the urethral sphincter. Three types of NO synthase (nNOS, eNOS and iNOS) are present in the lower urinary tract. Reports of NO dependent neurogenic relaxations of urethral preparations have been found in dog Takeda and Lepor, 1995, rat Parlani et al. 1993, pig Bridgewater et al. [10] and human Ethren et al. [11] Exogenously applied NO donors and NO to urethral preparations shows concentration -dependent relaxations [12]. NANC-mediated relaxation of bladder neck and urethral smooth muscle is associated with increased c-GMP levels [13]. Exposure of human and guinea pig isolated urethral sphincter preparations to NO donors has been shown to cause relaxation with associated increase in cGMP immunoreactivity in urethral smooth muscle cells Smet et al. 1996. Further, electrically stimulated relaxations in rabbit urethral preparation has been shown to be with increased intracellular cGMP level in urethral smooth muscle cells [14]. Inhibition of electrically stimulated relaxations was observed with NOS inhibitors which were also associated with inhibition of intracellular cGMP elevation.

It is interesting to note that most of these studies have been to investigate the function of NO on smooth muscle. Therefore, it is possible that striated muscle may also take part along with urethral smooth muscle in NO-dependent neurogenic relaxation in different species. Other observations suggest that NO has a role in the control of intramural striated muscle of the human male membranous urethra (Ho et al. 1998 and in the female urethral striated muscle Ho et al. 1999. Both NOS-immunoreactivity and NADPH-diaphorase activity are evident in the sarcolemma of the intramural striated muscle and in the nerve trunks and fine nerve fibres in human male and female urethral striated muscle. Thus, implication of NO with the sarcolemma suggests an inhibitory role in mediating relaxation of the striated sphincter of the membranous urethra during voiding phase of micturition.

In contrast to the urethral preparations showing relaxation effect with electric field stimulation, detrusor could not show any evidence for nerve- mediated relaxation. In rat bladder preparation, electric field stimulation is associated with frequency -dependent contractions which were not significantly influenced by NOS inhibitors [12]. Detrusor preparations from rabbits [15], humans [11] and sheep Garcia et al. [16] exhibited similar results. In contrast, electric field stimulation in human detrusor has shown minor relaxation under certain experimental conditions [17]. Exposure of bladder preparations to exogenous NO donors or NO is associated with smaller relaxation in rats [12], rabbits [14] and pigs [18]. Further, detrusor smooth muscle cells are less sensitive to the effects of cGMP [14]. Exogenous No donors have been found to evoke a complex response of relaxation, contraction or a transient relaxation followed by contraction in human detrusor [19]. An attenuated NO-mediated contraction with inhibition of soluble guanylyl cyclase in her study was suggestive of the fact that the NO-mediated contractility via cGMP might be due to involvement of interstitial cells. Detrusor interstitial cells have a morphological similarity to those of Cajal of digestive tract and have specialised pace making properties [19]. The relaxant response was not affected by guanylyl cyclase inhibitor rather, potentiated in presence of ibuprofen. Therefore, NO may be keeping the bladder relaxed during the filling phase of micturition. Indeed, a similar function of NO as a mediator of adaptive relaxation in the stomach to accommodate food or fluid has been observed [20].

Inactivation of the cGMP-dependent protein kinase gene (cGK1) in mice was shown to abolish the NO/cGMP-dependent relaxation of urethral smooth muscle with bladder instability which suggest that bladder instability may be associated with impaired NO/cGK 1 signalling pathway [21]. The activation of a c-GMP-dependent protein kinase was shown to hyperpolarize the cell membrane possibly by activating K+ channels [22]. Patch clamp studies using NO donor SIN-1 has shown activation of ATP-sensitive K+ channels in guinea pig urinary bladder smooth muscle cells mediated through a c-GMP/PKG dependent mechanism [23,24].

Conclusion

Ion channels play an important role in determining the properties of spontaneous contractile activity in the urethra and detrusor. An important physiologic role of NO in the relaxation of urethral sphincter during micturition has also been demonstrated both in vitro and in vivo experiments. In addition, during the filling phase of micturition, there might be a relaxant effect of NO on the detrusor. And it is apparent that NO has a definite role in the modulation of ion channel in the lower urinary tract. Therefore, NO pathway altering the channel function in modulating contractile activity of the lower urinary tract can be best exploited for the treatment of voiding dysfunction.

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