Antikolinerjik ilaçların mesane üzerinde ki etki mekanizması nedir – nörojenik mi yoksa non-nörojenik mi?

What is the mechanism of action of anticholinergics in the bladder – is it neurogenic or non-neurogenic?

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Özet

İnsan mesanesi, kompliansı yüksek, sinirsel desteği ise oldukça kompleks yapıda bir depolama organıdır. Bu bölgeyi innerve eden sinir sisteminin disfonksiyonu nörojen mesane olarak adlandırılmakta ve mesane fonksiyonlarını değişen derecelerde etkileyebilmektedir. Nörojen mesaneye bağlı oluşan semptomlar içerisinde yaşam kalitesini en çok etkileyeni idrar inkontinansı olarak bildirilmektedir. Nörojen mesanede idrar inkontinansı oluşumunun en önemli mekanizmlarından birisi ürodinamik çalışmada detrüsör aşırı aktivitesi ile izah edilmektedir. Oral antikolinerjik ilaçlar nörojen detrüsör aşırı aktivitesinin tedavisinde dönüm noktası olarak kabul edilirler. Bu derlemede nörojen mesane olgularında mesane kompliansını ve kapasitesini arttırmak ve istemsiz detrüsör kontraksiyonlarını azaltmak için kullanılan antikolinerjik tedavinin etki mekanizmasını analiz ettik.

Anahtar Kelimeler: antikolinerjik tedavi, detrüsör aşırı aktivitesi, nörojenik mesane

Abstract

The human urinary bladder is a highly – compliant storage device and nerve supply to the bladder is relatively complex. Dysfunction of the nervous system could affect the urinary bladder negatively, a condition called 'neurogenic bladder'. Among neurogenic bladder complications, urinary incontinence is the most significant factor in determining quality of life. Urinary incontinence in neurogenic bladder is explained by detrusor overactivity on urodynamic assessment. Oral anticholinergic medications are largely accepted as the cornerstone in the management of neurogenic detrusor overactivity. In this review article, we closely analyse the mechanism by which anticholinergic treatment help increasing bladder compliance and bladder capacity and reducec involuntary detrusor contraction in neurogenic bladder cases.

Key Words: anticholinergic treatment, detrusor overactivity, neurogenic bladder

Introduction

The human urinary bladder is a highly – compliant storage device that allows controlled voiding. It is formed of body and dome, base including trigone and bladder neck. Although bladder trigone is embryological and histologically distinct, it shows synchronous stimulation with other parts of the bladder to provide efficient bladder emptying (1).

To allow effective voiding, bladder smooth muscle (detrusor) contraction is achieved by cross bridging of myosin molecules in response to increased ATPase and myosin light-chain kinase enzymes. The whole process is induced by rise in intracellular calcium level (2). Nerve supply to the bladder is relatively complex. From the sacral spinal cord, pelvic parasympathetic signals relax the sphincter and contract the bladder. Lumbar sympathetic supply, on the other hand, is inhibitory to detrusor and excitatory to sphincter mechanism. Urethral sphincter is also stimulated by pudendal (somatic) nerve (3).

Accordingly, dysfunction of the nervous system could affect the urinary bladder negatively, a condition called 'neurogenic bladder'. The extent by which bladder functi-

on is compromised mainly depends on the location and nature of nervous system pathology (4). Well-known causes of neurogenic bladder include Parkinson's disease or multiple sclerosis, congenital or traumatic spinal cord damage and cerebral palsy.

This group of patients are generally prone to urinary sepsis, retention of urine and vesico-ureteric reflux with possible progression to hydronephrosis and subsequent renal failure, if left untreated (5). Urinary incontinence is another common complication of neurogenic bladder which is rather difficult to treat (6,7).

The ultimate aim in treating neurogenic bladder patients, therefore, is to maintain their kidney function, prevent urinary infections, reduce the risk of incontinence and eventually improve patient quality of life.(8) Among all, urinary incontinence is the most significant factor in determining quality of life (9).

Urinary incontinence in neurogenic bladder is explained by detrusor overactivity on urodynamic assessment which is characterised by the presence of 'spontaneous or provoked filling-phase detrusor contractions that are involuntary' (10).

Oral anticholinergic medications are largely accepted as the cornerstone in the management of neurogenic detrusor overactivity and their use, mechanism of action, adverse effects, multiple formulations and variable receptor selectively are extensively documented in the literature (11,12).

In this review article, we closely analyse the mechanism by which anticholinergic treatment help increasing bladder compliance and bladder capacity and reducec involuntary detrusor contraction in neurogenic bladder cases.

Main Body

Normal bladder physiology

In order to understand the mechanism by which antimuscarinics exert their effect on the bladder, detailed understanding of normal bladder physiology is necessary.

Bladder capacity, represented by the ability of the bladder to accommodate urine, is indicated by the distinct properties of detrusor muscle and bladder stroma and the suppression of efferent signal pathway from the bladder (3). The sympathetic activation of the sphincter mechanism is also a contributing factor (13).

Emptying phase of the bladder, on the other hand, is triggered by activated parasympathetic efferent nerves leading to detrusor contraction, accompanied by relaxation of the sphincter secondary to inhibition of sympathetic and somatic pathways (14). Voiding process is generally voluntary but could be involuntary in infants or patient with neurogenic bladder 'reflex voiding'.

Detrusor muscle contraction

In humans, at least 5 subtypes of muscarinic receptors are identified (M1 – M5) (15). Despite the fact that M2 receptors are most abundant in the bladder, M3 receptors are largely responsible for parasympathetic muscarinic detrusor contractions (16,17). Detrusor contraction is requires phospholipase C enzyme stimulation by acetylcholine leading to an increase in calcium levels intracellularly(18).

Following action potential and muscarinic receptor activation, Calmodulin, an intracellular protein, binds to calcium activating myosin light – chain kinase enzyme. The later is responsible for actin – myosin interaction within detrusor muscle and hence generation of forceful muscle contraction (19).

It has been claimed that M2 receptors, if activated, has a synergistic effect to M3 receptors activity (20). This is explained by the ability of M2 receptors to activate cation and inactivate potassium channels and suppress sympathetic firing leading to detrusor contraction.

The role of suburothelial cells in detrusor contraction

Beneath the urothelium in the urinary bladder lies interstitial cells, also called 'myofibroblasts'. These cells have been described for their role in detrusor contraction (21). Muscarinic M2 and M3 receptors are found on myofibroblasts and their level of expression is found to be related to severity of urgency in patients with unexplained detrusor overactivity (22). This clearly indicates the role of such cells – myofibroblast in the pathophysiology of overactive and neurogenic bladder (23).

Antimuscarinic agents – What are they and what do they do?

Broadly, antimuscarinics are either tertiary or quaternary amines with variable molecular characteristics (10). Interestingly, although most of antimuscarinic agents are degraded by the cytochrome P450 enzyme (CYP2D6 and CYP3A4), some still produce active metabolites that pro-

duce therapeutic effect (24).

Antimuscarinis are still considered the cornerstone in the treatment of overactive bladder and detrusor overactivity (10). Although large numbers of antimuscarinic medications are currently available, it is of note that a high placebo effect is shown on many studies (25). Nevertheless, based on large meta-analyses and available data, currently in-use antimuscarinic agents are significantly beneficial (26,27).

Problems arising form the use of antimuscarinic agents

Unfortunately, current antimuscarinic medications are not completely receptor – selective. Lack of receptor selectivity can result in unwanted side effects, rendering antimuscarinics less ideal medications. For instance, narrow angle glaucoma, if untreated, is an absolute contraindication for antimuscarinics' use (4). Also, antimuscarinic treatment can potentially result in serious cardiac and central nervous system side effects causing ventricular arrhythmia and cognitive dysfunction, dizziness or memory loss, respectively (24,28). Less serious but commoner known adverse effects of antimuscarinics include e, mouth dryness, blurry vision, headache and constipation (4).

It appears that even if a purely selective M3 – receptor antagonist is developed; it would still potentially causes problematic side effects. This is explained by the fact that M3 receptors readily available in the urinary bladder are morphologically and functionally similar to those located on other tissues (29).

Therefore, pharmaceutical companies are hunting for 'uroselective' rather than 'receptor – selective' antimuscarinic agent.

Mechanism of action of antimuscarinis – Neurogenic

Although large number of studies claimed beneficial effect of antimuscarinics in treating patients with neurogenic bladder, interestingly, it is still admitted that the exact mechanism by which antimuscarinics exert their therapeutic effect is not well understood yet (10)

For long years, it is largely thought that antimuscarinics mainly inactivate muscarinic receptors available on detrusor muscle fibres and eventually blocks parasympathetic nerve – induced acetylcholine release and detrusor muscle stimulation and contraction. Therefore, the general idea was that antimuscarinics are only effective on the emptying phase of the bladder (4).

In 2004, however, it is postulated that antimuscarinic agents actually improves bladder capacity and reduces urgency and urge incontinence by affecting bladder filling more than emptying (2).

Further study revealed that acetylcholine stimulates afferent neuronal pathway from the urinary bladder either directly or by exerting an effect on the detrusor muscle tone (indirectly) and antimuscarinics help to reduce this afferent nerves excitation (C and Aδ fibres) during bladder filling phase (30).

In 2006, a study on the effect of antimuscarinics on the bladder revealed that doses of antimuscarinic agent enough to reduce detrusor overactivity produce insignificant reduction in detrusor contraction. Thus, indirectly concluding that antimuscarinic medications have more pronounced sensory effect (bladder filling phase) (31).

Examples of antimuscarinics that has neurogenic – only mechanism in treatment of neurogenic bladder include, Atropine Sulphate, Propantheline Bromide, Trospium, Tolterodine Tartrate, Darifenacin Hydrobromide, Solifenacin Succinate and Fesoterodine Fumarate.

Atropine Sulphate is usually not recommended due to severe systemic adverse reactions. Intravesical preparations, however, can be used in cases of neurogenic bladder with an effect comparable to intravesical oxybutinin (32).

Another less favourable choice is Propantheline Bromide. The later is a non-selective antimuscarinic agent that has short half-life and low bioavailability (5% – 10%) (33). Therefore, no study probing the benefit of this medication has been carried out recently.

Trospium (non – selective antimuscarinic), on the other hand, is proved to be effective in neurogenic bladder management in randomized – controlled trials (34,35).

Although Tolterodine is a non – selective antimuscarinic medication, it is thought to have predilection to M receptors in the bladder 'functional selectivity' (36).

A relatively selective M3 receptor blocker is described, Darifenacin Hydrobromide (37). Multiple studies showed that Darifenacin is relatively safer in terms of possible cognitive or cardiac side effects than other antimuscarinics (38,39) Solifenacin Succinate is another antimuscarinic that is developed and described to be more selective to M3 receptors than M1 and M2 receptors (10)

Lastly within this group, Fesoterodine is an antimuscarinic and precursor for its active metabolite (5-hydroxymethyltolterodine) which is, in fact, similar to Tolterodine's metabolite (40). Significant proportion of 5 – hydroxymethyltolterodine is excreted in the urine unaffected. This indirectly suggests that Fesoterodine has a topical effect on the bladder urothelium in neurogenic bladder (41).

Mechanism of action of antimuscarinics – Non-neurogenic

Few of antimuscarinic agents, such as Terodiline and Oxybutinin Chloride, have more than one mode of action to improve bladder capacity in neurogenic bladder: potent antimuscarinic (neurogenic) activity and less clear 'direct' (non – neurogenic) detrusor muscle fibre relaxation (4).

Terodiline is no longer clinically available due to its possible serious cardiac side effect – polymorphic ventricular tachycardia (42).

Oxybutinin Chloride, a tertiary amine, is metabolized by the cytochrome P450 enzyme. Pharmacologically, Oxybutinin is an antimuscarinic, direct muscle relaxant and local anesthetic agent and it shows selectivity to M1 and M3 over M2 receptors (43).

In vitro, Oxybutinin is 500 times weaker direct muscle relaxant than as an antimuscarinic agent.[44] This fact suggests that oral Oxybutinin works mainly by its antimuscarinic effect and for it to produce muscle relaxation, intravesical preparations are to be used.

Although Oxybutinin is used intravesically in patients performing clean intermittent self – catheterisation (CISC), no unique intravesical preparation is available in the market. It is shown that part of intravesically – installed Oxybutinin is absorbed into the circulation (45). Unfortunately, the benefit related to local versus systemic absorption of Oxybutinin in intravesical instillation is not fully understood yet.

Hope for future:

A recent review article supported new 'hyperactive afferent pathway of the bladder' in causation of neurogenic bladder.[46] Further clinical studies targeting this pathway within the suburothelium to treat neurogenic bladder are required. By reducing afferent signals from the bladder, it is hoped that reflex voiding would potentially be delayed and hence improve bladder capacity without compromising detrusor contraction during voiding phase.

Also, more robust studies need to be in started to create enough evidence to allocate anitmuscarinics into groups according to their effectiveness in order to decide which of these groups are to be administered as first – line therapy for detrusor overactivity (27).

Conclusions

- Human urinary bladder is under strict neurological control. Disturbance in its neurological pathway results in neurogenic bladder. The extent and severity of neurognic bladder largely depends on the nature and location of nerve involvement.
- Antimuscarinic agents are still the mainstay treatment for overactive and neurogenic bladders and, therefore, all urologists need to be familiar with muscarinic receptors and their relative presence in different organs.
- Although the actual mechanism of action of antimuscarinics is not fully understood yet, to the best of our knowledge, the effect of most of today's antimuscarinic agents on neurogenic bladder is neurogenic and only few preparations have more than one mechanism of action – neurogenic and non-neurogenic.
- Ideal, new and no – side effects antimuscarinic agent is yet to be developed. A possible target is the suburothelial fibromyoblasts regulating the afferent pathway without exerting an effect on detrusor contractile element.

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