INTRODUCTION

Overactive bladder (OAB) is a syndrome characterized by the presence of urgency, with or without urinary incontinence usually with increased daytime or night-time frequency. OAB is a very prevalent condition in both female and male patients, and it is more common in older adults compared with the general population. Moreover, OAB syndrome adversely affects patient's health-related quality of life inducing depression, social isolation and decreased levels of activity, especially in presence of urgency incontinence ***(Abrams et al., 2009).***

The prevalence of overactive bladder (OAB) is high, with 12–16% of adults in Europe, USA affected by this symptom syndrome ***(Milsom et al., 2001).***

Urinary bladder smooth muscle is enriched with muscarinic receptors, the majority of which are of the M2 subtype whereas the remaining minority belong to the M3 subtype. Antimuscarinic agents, such as Solifenacin, are first-line pharmacotherapy for the treatment of OAB symptoms. However, some patients have a suboptimal response to antimuscarinics and some may experience intolerable side-effects, such as dry mouth and constipation ***(Benner et al., 2010).***

Recent advances in the understanding of OAB have identified three β-adrenoceptor subtypes, β_1, β_2 and β_3, in the detrusor muscle and urothelium ***(Kullmann et al., 2011).***

The β_3-adrenoceptor is the predominant β-receptor subtype in the human urinary bladder. β_3-adrenoceptor agonists relax detrusor smooth muscle during the bladder storage phase and increase bladder capacity without negatively affecting voiding parameters, including maximum urinary flow rate (Q_{max}), detrusor pressure at Q_{max} ($P_{det}Q_{max}$), and residual volume ***(Nitti et al., 2013).***

Recently, (Mirabegron) a new class of oral drug has emerged, which induces a direct relaxation of detrusor smooth muscle via stimulation of bladder β3-adrenoceptors and has been approved by the USA Food and Drugs Administration (FDA) and European Medicines Agency (EMEA) for treatment of OAB. In the USA and Canada, the recommended starting dose is 25 mg once daily, with an option to increase to 50 mg. In Europe and Japan, the recommended dose is 50 mg once daily with 25 mg dose reserved for special populations (e.g. those with renal or hepatic impairment) ***(Nitti et al., 2013).***

Aim of the Work

The Aim of this study is to compare effect of β-3 Androreceptor agonist (Mirabegron) versus M3 Antimuscarenic (Solifenacin) in patients with over active bladder symptoms as regards over active bladder symptoms score and Urodynamic study.

Chapter 1

NEUROANATOMY OF THE LOWER URINARY TRACT

1- Gross anatomy of the lower urinary tract

The LUT consists of two functional structures:

- A reservoir responsible for holding urine, called the bladder
- An outlet to release urine, consisting of the bladder neck, urethra, and external urethral sphincter ***(Beckel and Holstege, 2011).***

The bladder is a sac-like organ with a wall consisting of three layers of smooth muscle, called the detrusor. Lining the lumen of the bladder is a layer of transitional epithelium, called the urothelium, which forms an almost impermeable barrier, allowing the bladder to hold urine. Between the detrusor and the urothelium lies the submucosa and the lamina propria; layers of connective tissue that also house capillaries, afferent nerve terminals, lymph vessels, and immune cells. Urine is released from the bladder through an outlet, a tube of smooth muscle called the urethra ***(Beckel and Holstege, 2011).***

The urethra is surrounded by the striated muscles of the pelvic floor. That part of the pelvic floor which lies immediately around the urethra is known as the external

urethral sphincter. The urethra joins the bladder at its neck with a circular ring of smooth muscle called the internal urethral sphincter. During urine storage, both the internal and external urethral sphincter muscles are contracted, closing the bladder outlet thereby holding urine in the bladder ***(DeLancey et al., 2002).***

2- Peripheral innervation of the lower urinary tract

The LUT is innervated by three sets of nerves:

1- Parasympathetic sacral pathways that travel the pelvic nerve,

2- Sympathetic thoracolumbar pathways that travel the hypogastric nerve,

3- Sacral somatic motoneurons that travel the pudendal nerve ***(Fowler et al., 2008)***

These pathways work in concert in a reciprocal fashion to control the two functions of the LUT; storage being mediated through the sympathetic and somatic motoneurons, while voiding is induced via the parasympathetic pathways. Another important role is played by sensory afferent nerves, which carry information on bladder filling to the spinal cord ***(Fowler et al., 2008)***.

1- Sympathetic Pathways:

Sympathetic preganglionic motoneurons that innervate the bladder are located in the thoracolumbar levels of the spinal cord (T11–L2) of humans ***(C. de Groat 2001)***.

These neurons exit the spinal cord and pass along the paravertebral sympathetic chain to the inferior splanchnic nerve and the inferior mesenteric ganglion Although some fibers synapse on postganglionic neurons in the inferior mesenteric ganglion, most preganglionic fibers continue along the hypogastric nerve to terminate on postganglionic neurons in the pelvic ganglion of the major pelvic plexus. From there postsynaptic fibers innervate the bladder and urethra. Additionally, both the pelvic and pudendal nerves, at least in the rat and cat, contain postganglionic sympathetic fibers from the paravertebral chain ganglia ***(C. de Groat 2001)***.

The sympathetic innervation of the bladder is divided into two distinct groups, those that innervate the main portion of the bladder and those that innervate the bladder neck and the urethra. Of these two areas, the bladder neck and sphincter receive the strongest innervation. The postganglionic sympathetic fibers release norepinephrine to activate a adrenergic receptors which constrict the smooth muscle of the bladder neck and internal urethral sphincter. b-adrenergic receptors on the detrusor also receive sympathetic innervation,

and stimulation of these receptors causes relaxation of the detrusor smooth muscle ***(Morita et al., 2000).***

2- Parasympathetic Pathways:

From the spinal cord, preganglionic motoneurons send fibers along the pelvic nerve to release acetylcholine through synapses on postganglionic neurons in the pelvic plexus or continue on to intramural ganglia located in the wall of the bladder Postganglionic parasympathetic fibers release acetylcholine and ATP on smooth muscle fibers in the bladder by activating muscarinic (M3) and purinergic (P2X) receptors, respectively. Parasympathetic fibers of the pelvic nerve also innervate the smooth muscle of the internal urethral sphincter where they release nitric oxide (NO), which has an inhibitory effect ***(De Groat, 2006)***.

3- Somatic Pathways

The innervation of the striated muscle of the external urethral sphincter originates in a specific region of the lateral ventral horn of the sacral spinal cord, generally centered in the human at the S2 segment, but also in the caudal end of the S1 segment and the middle of S3 ***(Beckel and Holstege, 2011).***

4- Afferent Sensory Pathways

Sensory afferent nerves innervating the bladder and urethra travel along all three of the previously discussed nerves

(pelvic, pudendal, and hypogastric). Of these three nerves, pelvic afferents play the most significant role in LUT function ***(Yoshimura et al., 2003)***.

Bladder afferent nerves are comprised of two types, myelinated A–d fibers and unmyelinated C-fibers. Generally, these two subtypes of afferent nerves can be differentiated by the stimulus that activates them. A–d fibers respond to stretch of the bladder wall as the bladder fills with urine and to bladder contraction when voiding occurs, The threshold pressure to activate these fibers is relatively low; approximately 5–15 mm Hg, which corresponds to the pressure in the bladder when most humans first report sensations of bladder filling. C-fibers, on the other hand, are generally labeled as silent, as they have very high thresholds for firing and are not activated by physiologically relevant bladder pressures. C-fibers respond to nociceptive stimulation by chemicals, such as capsaicin or menthol, or in response to inflammation ***(Rong et al., 2002)***.

Additionally, chemical stimulation can sensitize C-fibers, allowing them to become mechanosensitive ***(Andersson, 2002).***

These findings suggest that the two types of afferent nerves perform separate roles in transmitting sensory information from the bladder; Aδ fibers transmit information on bladder filling to the central nervous system, while C-fibers, in case of pathological conditions in the bladder, signal

nociceptive information, leading to feelings of pain in the bladder or bladder sphincter ***(Andersson, 2002).***

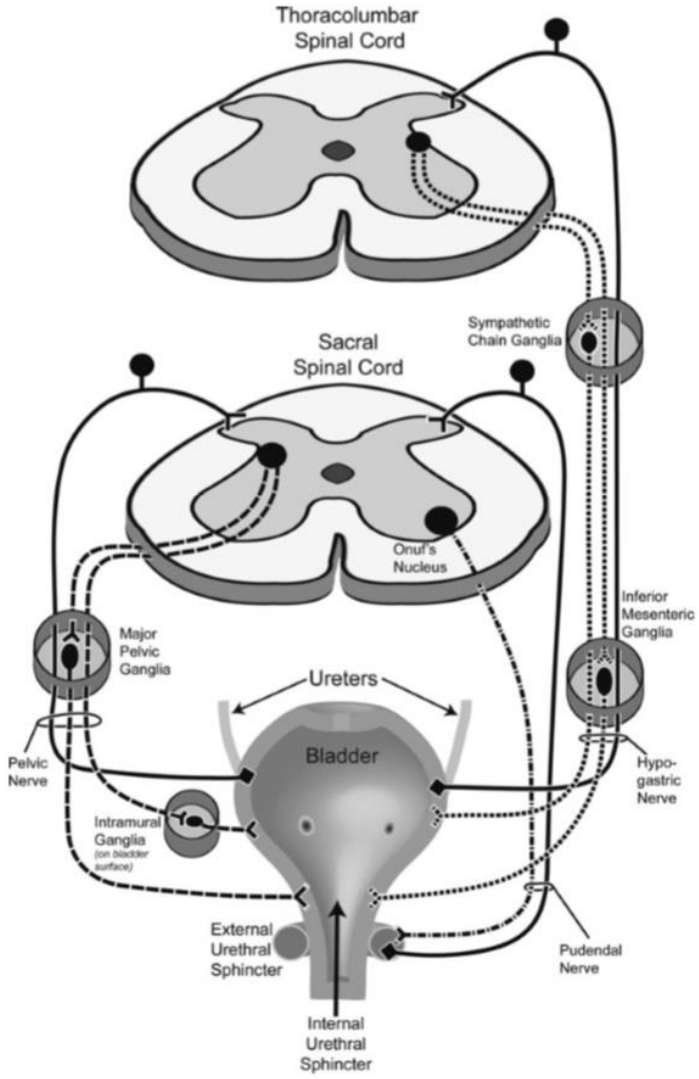

Figure (1): Peripheral innervation of the LUT. Diagram depicting the peripheral innervation of the lower urinary tract. Solid lines afferent nerve fibers; dashed lines parasympathetic pathways; Dotted lines sympathetic pathways; dashed with dots somatic motoneurons.

Muscarinic Receptor Subtypes in the Lower Urinary Tract

The muscarinic receptor occurs in 5 subtypes (M1 – M5) and the fundamental significance of muscarinic M3 receptors for micturition is well established ***(Uchiyama and Chess-Williams, 2004).***

Although it has been recognized for a long period of time that other subtypes of the receptor can be found on smooth muscle cells, when examined morphologically, the functional significance of the different receptor sub- types has not been fully unravelled ***(Tobin et al., 2009).***

It is well known that the subtypes of the receptor population interact on neuronal as well as on non-neuronal cells in the regulation of autonomic responses ***(Tobin et al., 2009).***

Lately, however, muscarinic receptors have also been suggested to be implicated in the control of inflammation, cell growth and proliferation ***(Casanova and Trippe, 2006).***

The muscarinic receptors belong to the family of G-protein-coupled receptors, The G proteins, consisting of one α, β and g -subunit,, are subdivided into G s, G i/o, G q and G 12 depending on the primary sequence homology of their α subunits ***(Zholos et al., 2004).***

The muscarinic receptor subtypes couple differentially to the G proteins, and the subunits of G proteins activate distinct cellular pathways. Preferentially, the inhibitory muscarinic M 2 and M 4 receptors couple to G i/o, whereas the excitatory muscarinic M 1, M 3 and M 5 receptors preferentially couple to G q/11 ***(Zholos et al., 2004).***

The inhibitory muscarinic M 2 and M 4 receptors may also affect adenylate cyclase activity, prolong the opening of potassium, as well as that of non-selective cation channels and transient receptor potential channels ***(Lucas et al., 2006).***

Muscarinic M 1, M 3 and M 5 receptors, on the other hand, increase intracellular calcium by mobilizing phosphoinositides that generate InsP3 (inositol 1,4,5-trisphosphate) and DAG (1,2-diacylglycerol) ***(Lanzafame et al., 2003).***

Detrusor muscle

The contraction of the urinary bladder is primarily dependent on the activation of muscarinic receptors. In the urinary bladders of different species, including man, mRNAs for all 5 muscarinic receptor subtypes are expressed ***(Sigala et al., 2002).***

In the human detrusor, Mansfield et al., reported that of the total muscarinic receptor population, 70% were of the M 2 subtype, 20% of the M 3 subtype and 10% of the M 1 subtype.

The dominance of muscarinic M2 receptors is consistently reported. So, the ratio between muscarinic M2 and M3 receptors in binding studies has been estimated as 9: 1 and 3:1 in rats and humans, respectively ***(Mansfield et al., 2005).***

Although in the minority, in several functional and knockout studies, the muscarinic M 3 receptors have been linked with the entire or almost the entire cholinergic contractile response of the bladder ***(Chess-Williams et al., 2001).***

Also, the muscarinic M 3 receptors induce the major part of the hydrolysis of phosphoinositide in the bladder,However, the muscarinic M 5 receptor protein closely resembles the protein of the muscarinic M 3 receptor and its pharmacological effect is hard to discriminate from that of other excitatory muscarinic receptors, particularly the M 3 subtype ***(Eglen et al., 2001).***

Although muscarinic M 3 receptors are principally responsible for the bladder contraction, in vivo knockout studies have revealed that muscarinic M 2 receptors may have direct but small contractile effects, However, prerequisites for direct muscarinic M 2 receptor involvement in contraction are inactivated muscarinic M 3 receptors and high levels of intracellular cAMP ***(Yamanishi et al., 2002).***

α1-Adrenoceptors

mRNA expression The presence of α1-adrenoceptor subtype mRNA in the urinary bladder has been assessed in rats, mice, monkeys and humans, with rats and humans apparently differing considerably. Using real-time PCR, other investigators confirmed a moderate expression of α1-adrenoceptor mRNA in the human bladder (corresponding to only 3% of β-adrenoceptor mRNA abundance), to which a1A-, a1B- and a1D-adrenoceptors contributed 33, 53 and 14%, respectively ***(Hampel et al., 2002)***.

Other studies reported a dominant abundance of α1A- and α1D-adrenoceptor mRNA with less, if any, α1B-adrenoceptor mRNA in the human bladder

α2-Adrenoceptors

mRNA and protein expression To the best of our knowledge, the presence of α2-adrenoceptor subtype mRNA in the bladder has not been reported. At the protein level, however, other studies have detected α2-adrenoceptors in the detrusor and bladder neck of rabbits ***(Gillespie, 2004)***.

β-Adrenoceptors

mRNA expression The presence of β-adrenoceptors in the rat and human bladder at the mRNA level has been studied using Northern blots, PCR and in situ hybridization. Messenger RNA for all three β-adrenoceptor subtypes has been detected in rats ***(Li, Li et al., 2003).***

It has been claimed that the β3- adrenoceptor may be the most abundant subtype, but no specific quantitative data were reported. Studies in the human bladder have also detected mRNA for all three β-adrenoceptor subtypes ***(Nomiya and Yamaguchi, 2003)***.

Based upon quantitative PCR experiments, it appears that the β3-adrenoceptor accounts for more than 95% of all β-adrenoceptor mRNA in the human bladder, the presence of β3-adrenoceptor mRNA in the human detrusor has also been confirmed in in situ hybridization studies ***(Nomiya and Yamaguchi, 2003).***

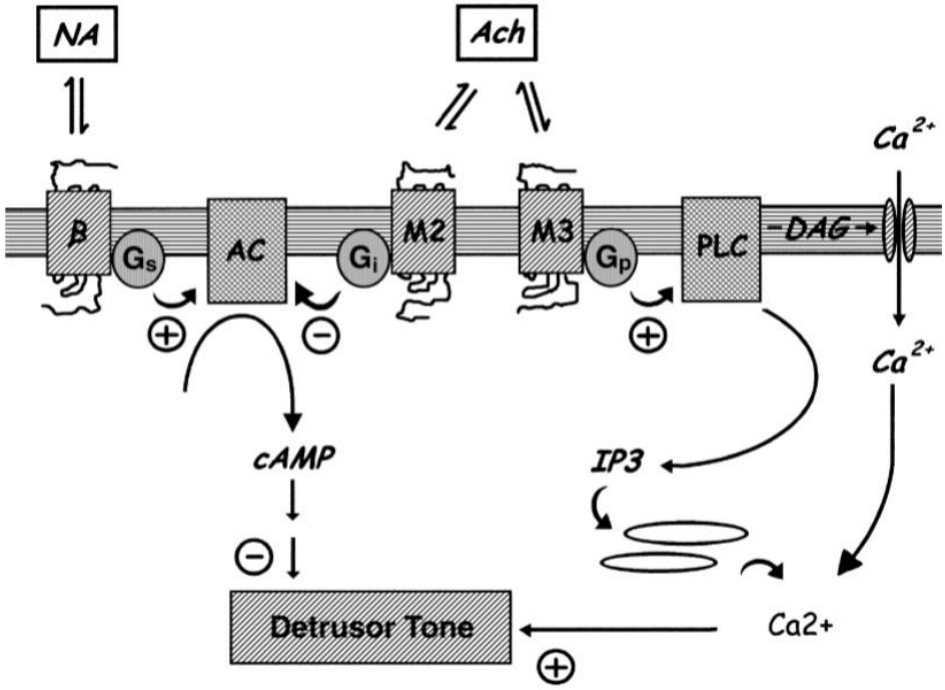

Figure (2): Muscarinic receptors of the detrusor muscle ***(Chess-Williams, 2002)***.

Chapter 2

PATHOPHYSIOLOGY OF OVERACTIVE BLADDER

Overactive bladder (OAB) is a common disorder that negatively affects the quality of life of our patients and carries a large socioeconomic burden.

It is characterized by urinary urgency with or without urge incontinence, with frequency and nocturia, without UTI. ***(Soligo et al., 2002)***

The pathophysiology of OAB:

The bladder stores urine until it is appropriate to initiate micturition in response to internal and external stimuli. Micturition involves the higher brain centers, the pons, the spinal cord, the peripheral autonomic, somatic, and sensory afferent innervation of the lower urinary tract as well as the anatomical components of the lower urinary tract itself. Malfunction of any of these components may contribute to the symptoms of OAB ***(Steers, 2002).***

Common signs exhibited by unstable bladders include a sudden increase in intravesical pressure at low volumes during the filling phase, increased spontaneous myogenic activity, fused tetanic contractions, altered responsiveness to stimuli,