News in neuro-urology

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Introduction

Overactive bladder (OB) is defined as a medical condition referring to symptoms of urgency and frequency, with or without incontinence, when appearing in the absence of local pathology or metabolic factors that would account for these symptoms. It is a chronic and debilitating condition more frequent in women that in men that may affect one fifth of the European adult population. Urgency is now emerging as the fundamental symptom that leads to an increased micturition frequency and to urgency incontinence. Definition of urgency is still problematic. Although referring to an intense desire to void that can not be deferred, it must be distinguished from urge, a normal sensation that may occur whenever bladder capacity is surpassed. Although primarily a sensation, it is unclear if its origin depends upon an abnormal bladder sensation, an abnormal processing of normal bladder sensation in the central nervous system or an abnormal activity of the detrusor smooth muscle. Concerning the later hypothesis, it should be recalled that OAB occurs frequently in conjunction with an overactive detrusor. However, in many OAB patients involuntary detrusor contraction can not be identified during filling cystometry. It is unclear if segmental activity of the detrusor muscle, although insufficient to increase bladder pressure but enough to stimulate sensory nerves may initiate urgency. It is, however, possible that each one of these three mechanisms account for the emergency of urgency, depending upon the condition underlying OAB.

Treatment of OAB

1) Blocking smooth muscle contractions at the neuromuscular junction

a) Anti-muscarinic drugs

Standard treatment of OAB is anti-muscarinic drugs administration. Acetylcholine is the major stimulus to detrusor smooth muscle contraction both in the normal and in the overactive bladder. Acetylcholine released from postganglionic parasympathetic neurons act on M2 and M3 muscarinic receptors present in the bladder. The M3 subtype, although making up less than one third of the total of the bladder muscarinic receptors, is the main mediator of detrusor contraction. Following acetylcholine binding, the M3 receptors activate the phosphoinositol cascade that, ultimately, leads to the accumulation of intracellular Ca++. The predominant M2 subtype, which inhibits the adenylate cyclase cascade, may further contribute to an effective detrusor contraction, reverting the relaxation mediated by b3-adrenoceptors. In addition, acetylcholine may also bind to pre-junctional M1 receptors and block its own release from the post-ganglionic parasympathetic endings. Therefore, muscarinic receptor blockade represents a major therapeutic option for OAB. Muscarinic receptors are not bladder specific. They are found in salivary glands, gastrointestinal tract, eyes, heart and CNS. This is the reason why muscarinic receptor antagonists cause widespread side effects, the most troublesome being

dry mouth. Oxybutinin, tolterodine and trospium chloride are the most extensively studied substances with anti-muscarinic properties in the treatment of OAB. Oxybutinin has higher affinity to M1 and M3 receptors. Tolterodine and trospium have no selectivity to any of the muscarinic receptors subtypes. Numerous randomised, double blind, placebo controlled studies assayed oxybutinin 5mg TID, tolterodine 2 mg BID or trospium chloride 10 mg BID on patients with detrusor hyperreflexia or instability. All them significantly reduce micturition frequency and the number of episodes of urinary incontinence, increase maximal cystometric capacity and reduce maximal detrusor pressure. Oxybutinin has the worse tolerability, dry mouth being the most frequent side effect. Treatment discontinuation was reported in more than 80% of patients. Solifenacin, a M3 specific antimuscarinic compound, may represent a real improvement in this field. In a recent comparative study solifenacin was more effective than placebo and tolterodine in reducing frequency and episodes of urgency incontinence. In addition solifenacin, in contrast with tolterodine, also reduced urgency intensity. Solifenacin seems to have some degree of bladder specificity as the blockade of salivary glands is less than that caused by classical non-specific antimuscarinic drugs.

b) BTX

Another alternative to prevent acetylcholine dependent detrusor contractions is to block the release of this neurotransmitter from bladder post-ganglionic parasympathetic neurons. Botulinum-A toxin is a selective blocker of acetylcholine release from all cholinergic endings. Injection of 200-300 units of botulinum-A toxin in the detrusor (in 20-30 different sites) of NDO patients emptying the bladder by CIC was shown to cause bladder paralysis. In consequence, an increase in the volume to first detrusor contraction and maximal cystometric capacity and a decrease of maximal detrusor pressure occurred. Episodes of autonomic dysreflexia were reduced or even abolished in susceptible patients. However, although continent for several months, patients needed repeated injections of BTX-A every 6-9 months.

More recently 100-200 BTX-A injections were also assayed with considerable success in patients with non-neurogenic forms of bladder overactivity. Surprisingly, bladder retention was a rare event. Future studies will indicate the role of BTX in non-neurogenic OAB.

2) Increasing bladder relaxation

The normal detrusor relaxes under noradrenaline stimulation of b3 adrenoceptors. When available, specific b3–agonists might, therefore, be useful on patients with OAB. Moreover, recent experimental studies have shown an increased expression of a1D adrenoceptors in the body of chronically obstructed bladders. This suggests that a1-D blockers are useful in the treatment of selected cases of OAB, like those associated with chronic bladder outlet obstruction. As a matter of fact, in models of bladder out let obstruction using a suture around the bladder neck, a-blockers with affinity to a1 A and D receptors could decrease micturion frequency in spite of the maintenance of the urethral suture

3) Reducing bladder sensory input conveyed to the central nervous system

Experimental studies have shown that after chronic spinalization or after prolonged obstruction to bladder emptying, bladder C-fiber input is enough to activate the micturition reflex. The interruption of the Ad-fiber dependent neuronal pathways connecting the sacral spinal cord with the pontine micturition center after spinalization or the increased production by the hypertrophied bladder of trophic factors capable of sensitizing C-fibers have been pointed out as possible mechanisms for the increased C-fiber activity. Capsaicin, the pungent extract of chili peppers and resiniferatoxin (RTX), an extract of Euphorbia plants, both decrease C-fiber sensory input. Such property, known as desensitization, is due to the activation of a receptor almost exclusively present in sensory C-fibers of mammals including man known as the vanilloid receptor type 1 or TRPV1.

The blockade of bladder C-fiber input in man was first tried with capsaicin. However, the pungency of capsaicin impedes its use on patients with normal bladder sensibility. RTX, in contrast with capsaicin, was shown to be innocuous to man during intravesical application. In 50-100 nM solutions, RTX applied during 30 minutes to the bladder mucosa of patients with NDO increased volume to first contraction and

maximal cystometric capacity and decreased the number of incontinence episodes. The effect of one single instillation could last more than 6 months. RTX was recently assayed with equal success in the treatment of patients with idiopathic detrusor overactivity and in patients with OAB and benign prostatic hyperplasia.

An interesting aspect recently revealed by experimental studies is the capacity of urothelial cells to release ATP upon stretch or chemical irritation. ATP bind to P2X3 purinergic receptors in type C sensory fibers leading to bladder overactivity. Thus future compounds able to block P2X3 receptors may reveal extremely effective in treating OAB symptoms.

4) Modulating central nervous system pathways involved in micturition.

Baclofen is a $GABA_B$ receptor agonist that decreases the release of excitatory neurotransmitters from sensory fiber endings in the spinal cord. In theory this may depress the activation of the bladder pre-ganglionic parasympathetic neurons by sensory input. However, oral baclofen has demonstrated poor efficacy in the treatment of neurogenic and non-neurogenic OAB patients**.** In part, the lack of efficacy of baclofen may be ascribed to the poor CNS penetration of baclofen as intrathecal administration of the drug significantly increases the volume to first micturition and maximal cystometric capacity and a decreases the maximal detrusor pressure in spinal OAB patients. New CNS inhibitors effective by oral route may, therefore, be worth to investigate in the future. As an example, gabapentine, an oral anti-epileptic drug, was found effective in reducing micturition symptoms and increasing volume to first involuntary detrusor contraction and maximal cystometric capacity in NDO patients.

5) Increasing urethral resistance

Mixed incontinence is a common symptom. In many cases it is believed that leakage of small amounts of urine into the urethra during sudden intra-abdominal pressure rises triggers urgency and urgency incontinence. Thus, reducing urine leakage may improve the OAB component of urinary incontinece in such patients. To support this hypothesis, surgical procedures used for the treatment of stress incontinence were shown to reduce episodes of urgency incontinence in patients with mixed urinary incontinence. Duloxetine, a potent and selective setotonin and noradrenaline reuptake inhibitor, significantly increases urethral activity in cats. In a placebo controlled study, female patients with mixed urinary incontinence (predominantly stress) found a decrease in the number of incontinence episodes and an improvement of quality of life. Future studies will indicate the role of duloxetine in pure OAB patients.