

How Drugs Modify The Micturition Reflex: A Review

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Micturition is the process of expelling urine from the body via the bladder and urethra. Disorders of micturition such as Overactive Bladder and Urge Incontinence affect many people and the first-line treatment is drug therapy. In this review the current standard drugs, anti-muscarinics, are critically assessed against newer drugs and drug targets, some of which are still in experimental stages.

Micturition – the classical term for urination - is a complex action which relies on both the lower urinary tract and the micturition areas of the central nervous system (CNS) working together. It is comprised of two phases: storage, where urine from the kidneys is stored in the bladder until it is appropriate, and voiding where the urine is expelled from the bladder via the urethra. The detrusor is the smooth muscle of the bladder which is distended upon filling and is contracted during voiding. The outlet comprises the bladder neck along with the smooth and striated urethral sphincter muscles. The outlet is contracted during filling and relaxed during voiding [1].

The bladder is controlled by the CNS, both voluntarily through the somatic nervous system and also unconsciously through the two anatomical divisions of the autonomic nervous system. The sympathetic branch, when active, triggers the “fight or flight” response to danger and the parasympathetic branch allows us to relax and digest our food.

Nerves from the bladder to the CNS convey bladder filling via stretch receptors in the bladder wall along with pain and temperature via receptors for noxious stimuli. Central control of micturition comes from the Pontine Micturition Centre and the Periaqueductal Gray in the Pons with higher voluntary functions located in the fore-brain [2].

Disorders of micturition can be categorised into storage and voiding (incontinence) symptoms. Of most interest is the storage symptom Overactive Bladder (OAB), and the diagnosis of Detrusor Overactivity (DO). The 4th International Consultation on Incontinence defines Overactive Bladder as having the storage symptoms of urgency with or without urge incontinence and is usually demonstrated by a high frequency of urination episodes per day [3]. Detrusor Overactivity is defined as involuntary detrusor contractions during the storage phase of micturition. A patient with DO will feel the need to urinate regardless of how much urine is in the bladder. DO is diagnosed through invasive testing of bladder pressure [4]. DO is not synonymous with OAB, as only 69% of male and 44% of female OAB sufferers have DO [5]. Pharmacological treat-

ment is the first course of action for these symptoms, which can be abated theoretically by increasing bladder capacity, reducing detrusor activity and strengthening outlet sphincter resistance [2]. Therefore, a patient's micturition may be modified with drugs, hopefully to improve their quality of life.

In this paper I will outline the pharmacology, efficacy and safety of the current standard drugs (antimuscarinics) for OAB and DO as well as several novel drugs where research is still ongoing, targeting both the periphery and the central nervous system, using as current data as possible.

Peripheral Targets

Antimuscarinics

The parasympathetic branch of the autonomic nervous system is the main drive of bladder contraction. Nerve terminals release the transmitter chemical acetylcholine for which there are specific receptors on the detrusor muscle. Activation of these receptors causes contraction [6]. Antimuscarinic drugs block these receptors and so reduce the frequency of contractions. They are the current front-line treatment of bladder disorder [3], and have been shown to be safe, effective and well tolerated for DO and OAB. A Cochrane review analysing the results of several different clinical trials by Nabi [7] compared antimuscarinics with placebo and showed statistically significant improvements of OAB symptoms. However, they have a side effects due to lack of receptor specificity (there are similar receptors all throughout the body and these will be blocked too), the most common being dry mouth. This is shown in 31% of patients which can lead to poor compliance. The most recent antimuscarinic on the market, fesoterodine (currently being heavily marketed on the underground by Pfizer) has been shown to be superior at reducing the frequency of urges to its predecessor tolterodine with fewer instances of dry mouth [8]. However Chapple goes on to suggest that “the ceiling may have been reached for therapeutic efficacy”.

Botulinum

A toxin, botulinum inhibits acetylcholine release for up to 6 months after injection, decreasing detrusor contractility [9]. The most common subtype of botulinum toxin used in urology is botulinumtoxinA. It has shown to reduce the frequency of urge incontinence compared to placebo

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when injected into the detrusor muscle [10]. The above study mentions urinary retention and urinary tract infection (UTI) as adverse effects in a minority of cases. However the most recent study of over 400 women with DO against placebo showed positive results in reducing DO with a 31% incidence of UTI and a 16% incidence of urinary retention resulting in self-catheterisation [11]. Lucioni has shown it also inhibits sensory neurotransmitter release, which may explain its effect on decreasing urgency [12]. BotulinumtoxinA is still not licensed for intravesical injection in the UK but is used off-label.

β_3 adrenoceptor agonists

Sympathetic nerves on the bladder release the transmitter chemical noradrenaline, which causes relaxation via specific receptors on the detrusor, the most common subtype being the β_3 [13]. YM178 (Mirabegron), activates these receptors to increase bladder capacity during storage without affecting the voiding bladder contraction which can occur in antimuscarinics. It compared favourably in a random controlled trial against placebo and tolterodine and has passed phase III clinical trials [14]. The common side effects are headache and gastrointestinal effects [15].

CNS targets

Tramadol

An already well-known and widely used opioid analgesic (painkiller), tramadol has been shown to cause an increase in bladder storage capacity in conscious rats through a complex mechanism [16]. In humans bladder capacity and compliance were increased with no ill-effect upon voiding when administered epidurally, in contrast to other opioids such as morphine which cause urinary retention, an adverse side effect [17]. Singh also suggests tramadol would be useful in treating post-operative pain as the lack of urine retention would negate the need for catheterisation and so improve patient comfort. Research is still ongoing and tramadol has a large range of side-effects, the most common being nausea, as well as the method of administration favoured by Singh being impractical for most patients.

Gabapentin

Although originally developed as an analogue of the neurotransmitter *gamma*-aminobutyric acid (GABA), it doesn't have any effects on GABA receptors. Instead it is believed to be active on specific calcium channels [18]. Carbone et al showed that gabapentin reduced detrusor activity in patients with brain-derived bladder disorders [19]. Ansari et al showed gabapentin orally administered to children with OAB who were unresponsive to antimuscarinic drugs increased bladder capacity and reduced frequency of contractions [20]. Both studies showed few adverse side effects but they both had very small sample sizes.

Cizolirtine

Found to be a more potent analgesic than aspirin, Cizolirtine's mechanism of action is still controversial but it is

believed to modulate the release of two signalling molecules in the spinal cord, substance-P and calcitonin gene-related peptide (CGRP) [21]. A dose-finding study of patients with clinical OAB and/or urodynamic DO showed a "clear improvement" in urination frequency with orally-administered cizolirtine [22]. A phase II clinical trial showed cizolirtine to perform very similarly to the antimuscarinic oxybutynin in increasing bladder capacity and decreasing frequency of urination compared to placebo, albeit with its own side effect profile, mainly gastrointestinal effects [23].

I hope this essay has shown the breadth and diversity of current pharmacological research in treating OAB and DO. Although all of the research on the "alternative" drugs heavily disparages antimuscarinics for their side-effects, there still seems to be no better treatment as yet due to adverse effects and the difficulty of selectivity through oral administration.

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