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THE OVERACTIVE BLADDER: PHARMACOLOGIC BASIS OF DRUG TREATMENT

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ABSTRACT

Objectives. To provide an overview of the basis for drug treatment of the overactive bladder.

Methods. Published information is evaluated.

Results. The causes of bladder overactivity are not known, but theoretically, increased afferent activity, decreased inhibitory control in the central nervous system (CNS) or peripheral ganglia, and increased sensitivity of the detrusor to efferent stimulation may be involved. Several CNS transmitters can modulate voiding, but few useful drugs with a defined CNS site of action have been developed. Drugs that stimulate γ-aminobutyric acid receptors are used clinically. Potentially, drugs affecting opioid, 5-hydroxytryptamine, norepinephrine, dopamine, and glutamatergic receptors and mechanisms can be developed, but a selective action on the lower urinary tract may be difficult to obtain. Traditionally, drugs used for treatment of bladder overactivity have had a peripheral site of action, mainly efferent neurotransmission or the detrusor itself. Antimuscarinic drugs, β-adrenoceptor agonists, α-adrenoceptor antagonists, drugs affecting membrane channels, prostaglandin synthetase inhibitors, and several other agents have been used with limited success. New information on the α-adrenoceptor and muscarinic receptor subtypes in the human detrusor has emerged and may be the basis for the development of new compounds with effects on bladder overactivity. Decreasing afferent activity seems an attractive therapeutic approach, and drugs affecting afferent nerves by causing release of tachykinins, such as capsaicin and analogs, as well as agents blocking tachykinin receptors, may be of therapeutic interst.

Conclusions. New drugs, specifically designed for the treatment of bladder overactivity, are desirable.

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To effectively treat the overactive bladder, identification of suitable targets for pharmacologic intervention is a prerequisite. With the present knowledge of the central[1] and peripheral[2] control of micturition, sites and drug mechanisms that can influence bladder function can easily be identified. However, the problem is not only to inhibit bladder contraction, but to eliminate overactivity without disturbing normal micturition. Even if this might be possible, there is also a selectivity problem: how to affect bladder function without interfering with the function in other organ systems. In many cases of urinary incontinence (UI) associated with the overactive detrusor, the clinical therapeutic problem is twofold: urine leakage and lower urinary tract (LUT) symptoms. Overactive detrusor function may or may not be associated with LUT symptoms or urine leakage, and the relations between these factors are far from clarified.

Below, the pharmacologic basis for some of the current therapeutic alternatives for treatment of bladder overactivity, and possible future developments, are briefly discussed.

IDENTIFICATION OF DRUG TARGETS

As discussed in detail elsewhere,[1] several reflexes are involved in the storage of urine and in voiding. During storage, at low levels of vesical afferent activity, spinal reflexes are active mediating contraction of urethral sphincter mechanisms through somatic (striated muscle) and sympathetic (smooth muscle) nerves. Sympathetic nerves may also mediate detrusor and ganglionic inhibition. There is no activity in the sacral parasympathetic outflow. Micturition is initiated by distention of the bladder, activating mechanoreceptors in the bladder

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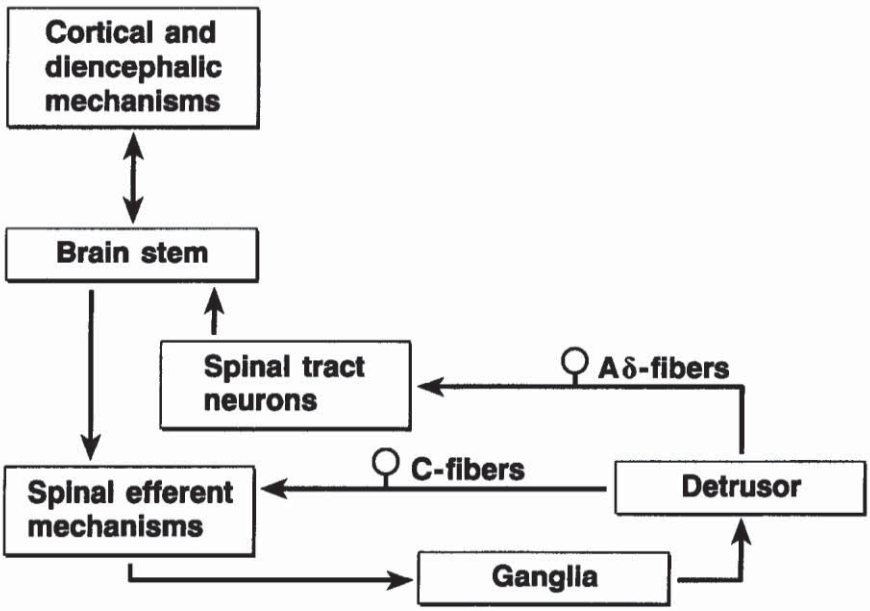

FIGURE 1. *Micturition reflex pathways. Based on de Groat et al.*[1]

wall. This triggers a high level of activity in small myelinated afferent nerves (Aδ), which via the dorsal root ganglia reaches the lumbosacral spinal cord (Fig. 1).[1] The A δ afferents connect to a spinobulbospinal reflex consisting of an ascending limb from the lumbosacral spinal cord, an integration center in the rostral brain stem (which is known as the pontine micturition center [PMC]), and a descending limb from the PMC back to the parasympathetic nucleus in the lumbosacral spinal cord. Afferent information may also be conveyed by small unmyelinated (C-fiber) vesical afferents, which have a high mechanical threshold but may be activated by irritation of the bladder mucosa. They may also be active in spinal cord injuries. Efferent micturition reflex pathways reach the bladder through the pelvic nerves.

CAUSES OF BLADDER OVERACTIVITY

There is still no consensus about the reasons for developing bladder overactivity. Theoretically, there may be 1) increased afferent activity, 2) decreased inhibitory control in the central nervous system (CNS) or in peripheral ganglia, 3) increased sensitivity to efferent stimulation in the detrusor, or a combination of these factors. Brading and Turner[3] proposed that all cases of detrusor overactivity (idiopathic, neuropathic, and obstructive) have a common feature—a change in the properties of the smooth muscle of the detrusor, predisposing it to unstable contractions—and that this change is caused by a reduction in the functional motor innervation of the bladder wall. They also stressed that bladder instability, as shown in a pig model of obstruction, may occur without participation of a micturition reflex. It seems difficult, however, to accept that a primary change in the detrusor should be the cause of the bladder overactivity seen in, for example, stroke patients. Even if the pathogenesis of bladder overactivity is unknown (and most probably is different in patients with outflow obstruction, neurogenic bladders, and idiopathic detrusor instability [DI]), drug targets for treatment of UI may be found peripherally or in the CNS.

CNS TARGETS

Anatomically, several CNS regions may be involved in micturition control: supraspinal structures, such as the cortex and diencephalon, midbrain, and medulla, and also spinal structures.[1] Several transmitters are involved in the micturition reflex pathways and may be targets for drugs aimed at control of micturition. However, few drugs with a CNS site of action have been developed. Drugs that stimulate γ-aminobutyric acid (GABA) receptors are used clinically. The potent inhibitory effects by opioids are well known, but have not been used therapeutically. Potentially, drugs that affect GABA, opioid, 5-hydroxytryptamine (serotonin), norepinephrine, dopamine, and glutamic acid receptors and mechanisms can be developed, but a selective action on the LUT may be difficult to obtain.

GABA

Both $GABA_A$ and $GABA_B$ receptor agonists suppress spinal and supraspinal components of the micturition reflex, and there are reasons to believe that in some species the supraspinal micturition

reflex pathway is under a tonic GABA-ergic inhibitory control.[1] The $GABA_B$ agonist baclofen is considered to depress monosynaptic and polysynaptic motor neurons and interneurons in the spinal cord and has been used in voiding disorders, including detrusor hyperreflexia secondary to lesions of the spinal cord.[4] The drug may also be an alternative in the treatment of idiopathic detrusor overactivity.[5] However, published experience with the drug is limited. Intrathecal baclofen may be useful in patients with spasticity and bladder dysfunction and may increase bladder capacity.[6–8] The therapeutic potential in bladder overactivity of the new generation of antiepileptic drugs, which are able to enhance GABA-ergic transmission by, for example, inhibition of GABA reuptake or GABA-transaminase,[9] would be worth investigating.

Enkephalins

Enkephalinergic varicosities are prominent in the regions of the spinal parasympathetic nucleus and the PMC, and enkephalins effectively depress micturition and sphincter reflexes by stimulation of μ-, δ-, and κ-receptors.[1] It is well established that morphine and other opioids depress micturition, and that this effect can be blocked by naloxone. However, so far drugs with effects on opioid receptors do not seem to have been developed for the treatment of bladder overactivity in humans.

Serotonin

The lumbosacral sympathetic and parasympathetic autonomic as well as sphincter motor nuclei receive a dense serotonergic input from the raphespinal pathway.[1] Drugs interfering with serotonin or with serotonin receptors have not been systematically tested as a treatment of the overactive bladder in humans. Whether or not imipramine, which among other effects blocks the reuptake of serotonin, depresses bladder overactivity by this mechanism,[10] has not been established.

Norepinephrine

Sympathetic, parasympathetic, and somatic nuclei in the lumbosacral spinal cord receive inputs from noradrenergic neurons in the brain stem. Bladder activation through these bulbospinal noradrenergic pathways may involve excitatory α_1-adrenoceptors.[11] Both in normal rats and in rats with bladder hypertrophy secondary to outflow obstruction undergoing continuous cystometry, doxazosin, given intrathecally, decreased micturition pressure.[12] The effect was much more pronounced in the animals with hypertrophied/overactive bladders. Doxazosin did not markedly affect the frequency or amplitude of the unstable contractions observed in obstructed rats. It was suggested that doxazosin may have an action at the level of the spinal cord and ganglia, thereby reducing activity in the parasympathetic nerves to the bladder, and that this effect was more pronounced in rats with bladder hypertrophy than in normal rats. Whether or not a spinal/supraspinal site of action contributes to the relief of symptoms, including bladder overactivity, produced by α_1-adrenoceptor antagonists in patients with benign prostatic hypertrophy (BPH),[13] remains to be established.

Dopamine

It is well known that patients with Parkinson's disease may have detrusor hyperreflexia, possibly as a consequence of nigrostriatal dopamine depletion and failure to activate inhibitory dopamine D1 receptors.[14] However, other dopaminergic systems may activate D2 receptors, facilitating the micturition reflex. Thus, Sillen *et al.*[15] showed that apomorphine, which activates both D1 and D2 receptors, induced overactivity in anesthetized rats via stimulation of central dopaminergic receptors. The effects were abolished by infracollicular transection of the brain and by prior intraperitoneal administration of the centrally acting dopamine receptor blocker spiroperidol. Kontani *et al.*[16,17] suggested that the bladder overactivity induced by apomorphine in anesthetized rats resulted from synchronous stimulation of the micturition centers in the brain stem and spinal cord, and that the response was elicited by stimulation of both dopamine D1 and D2 receptors. Whether or not drugs that block dopamine receptors can be used for treatment of bladder overactivity has not been established.

Glutamic Acid

N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamatergic receptors seem to play an essential role at excitatory synapses in the descending pathway from the PMC to the spinal parasympathetic nucleus.[11] In adult anesthetized rats, inhibitors of NMDA or AMPA receptors depress the amplitude of reflex bladder contractions and inhibit voiding. In unanesthetized animals, on the other hand, NMDA receptor antagonists decrease the volume threshold for inducing bladder reflex contractions and facilitate micturition. The potential role of drugs acting on glutamatergic receptors for control of bladder overactivity needs further study.

PERIPHERAL TARGETS

Anatomically, drug targets for treatment of bladder overactivity may be the bladder, urethra, prostate, ganglia, or peripheral nerves. The mechanisms most often aimed at are receptors or ion

channels known to be involved in the control of bladder contraction, for example, muscarinic receptors and L-type calcium channels. Other mechanisms involved in neurotransmission or in the excitation-contraction coupling of the detrusor smooth muscle may also be targets for pharmacologic interventions.

Muscarinic Receptors

Antimuscarinic drugs are still the most widely used treatment of urge, sensory, and motor urge incontinence.[4] However, the currently used drugs lack selectivity for the bladder,[18] which limits their usefulness. Theoretically, agents with selectivity for the bladder might be obtained if the subtype(s) mediating bladder contraction, and those producing the main side effects of antimuscarinic drugs, were known.

Several subpopulations of muscarinic receptors have been identified, and at least five different subtypes (m_1–m_5) have been cloned. Pharmacologically, four different subtypes (M_1–M_4) have been defined,[18] all with a wide distribution in the body. The subtypes that can be demonstrated in the human bladder, and those responsible for bladder contraction, have been studied using various approaches. Cultured human detrusor cells expressed M_3 receptors linked to phosphoinositide hydrolysis,[19] and an important role for M_3 receptors is widely accepted. The M_1, M_2, and M_3 receptor subtypes were demonstrated in human detrusor muscle by receptor binding; there was a distinct predominance of M_3 receptors.[20] However, Yamaguchi *et al.*[21] were able to demonstrate the presence of mRNA encoding the m_2 and m_3 subtypes, but not the m_1, m_4, and m_5 subtypes, in human bladder. Using subtype-specific immunoprecipitation, Wang *et al.*[22] could demonstrate only m_2 and m_3 subtypes in human and rabbit detrusor membranes, the ratio of m_2 to m_3 being 3:1. Despite a predominance of m_2 receptors in rabbit and rat detrusor, several investigators have found that the pharmacologically defined M_3 receptor mediates contraction.[22,23] Recently, however, M_2 receptors were also shown to be able to mediate rat bladder contraction in vitro as well as in vivo by reversing β-adrenoceptor–mediated relaxation.[24] Future studies with muscarinic receptor antagonists with a selectivity for M_3 receptors, such as darifenacin[25,26] and vamicamide,[27,28] will reveal whether or not the principle of selective M_3 receptor antagonism offers therapeutic advantages. Since M_3 receptors are located not only in the bladder, but also in the salivary glands and the intestine, this could mean that two of the most common side effects, dry mouth and constipation, will not be avoided. However, selective muscarinic receptor antagonists, such as zamifenacin, may be able to distinguish between M_3 receptors in different smooth muscles.[29] Tolterodine[30] lacks selectivity for muscarinic receptor subtypes, but still shows selectivity for the bladder over the salivary glands in an animal model, and possibly in humans.[31]

Muscarinic receptors, which on stimulation inhibit transmitter release, have been demonstrated on cholinergic nerves in rat bladder.[2] In this organ, three types of cholinergic receptors were demonstrated to affect acetylcholine release.[32,33] M_2 inhibitory receptors dominated in untreated preparations, whereas in physostigmine-treated bladder strips, where the concentrations of acetylcholine were elevated, facilitatory M_1 and nicotinic receptors were also demonstrated. Physostigmine had a biphasic effect, causing inhibition of acetylcholine release at low (M_2) and facilitation at high (M_1) concentrations. The authors suggested that even if muscarinic inhibitory receptors appear to be the only type activated by acetylcholine released by electrical stimulation under normal conditions, facilitatory receptors may be activated by the high-frequency parasympathetic nerve discharge that occurs during micturition. Particularly in pathologic conditions, such as the neurogenic hyperreflexic bladder, a mechanism like this may contribute to changes in bladder function. Antagonism of M_1 receptors may contribute to bladder inhibition.

Detrusor denervation as a consequence of outflow obstruction has been demonstrated in pigs and humans.[34,35] In detrusor from pigs with experimental outflow obstruction, Sibley[36] found that the response to intramural nerve stimulation was decreased. There was, however, a supersensitivity of the detrusor, including a leftward displacement of the concentration-response curve for acetylcholine. Sibley[36] suggested that this was due to partial denervation of the bladder as a result of the obstruction, and that one consequence of the supersensitivity might be DI. Further supporting the presence of cholinergic denervation in the bladders of obstructed patients with bladder instability, Harrison *et al.*[37] found that in detrusor strips from such patients, the acetylcholine concentration-response curve was significantly shifted to the left, suggesting an increased sensitivity to acetylcholine. On the other hand, Yokoyama *et al.*[38] found that the responses to acetylcholine of detrusor strips from patients with bladder instability were not significantly different from the responses of strips from patients without instability. The reasons for these conflicting results are unclear.

It might be assumed that the muscarinic receptor functions also change in nonobstructed bladders showing overactivity. Kinder and Mundy[39] compared detrusor muscle from human normal, idiopathic unstable, and hyperreflexic (neurological damage) bladders. They found no significant dif-

ferences in the degree of inhibition of electrically induced contractions produced by tetrodotoxin and atropine between detrusor strips from any of these bladders, and no significant differences in the concentration-response curves for acetylcholine. In overactive bladders without associated neurologic disorders, a decreased number of muscarinic receptors has been demonstrated,[40] but its relation to overactivity remains unclear. Isolated detrusor strips from patients with detrusor hyperreflexia were supersensitive to both carbachol and KCl, but responded like normal controls to intramural nerve stimulation. The results were interpreted to suggest a state of postjunctional supersensitivity of the detrusor secondary to a partial parasympathetic denervation of the detrusor.[41]

The muscarinic receptors remain a main target for drugs used to treat the overactive bladder. However, the complexity of muscarinic receptor functions in the bladder and elsewhere in the body makes it difficult to predict the optimal profile of subtype selectivity of antimuscarinic drugs meant for treatment of bladder overactivity.

Adrenoceptors

The role of the sympathetic nervous system in human bladder function has been much discussed, partly because of the paucity of the adrenergic innervation of human detrusor muscle. There is no doubt, however, that norepinephrine is released on electrical stimulation of human bladder tissue. In detrusor muscle from several species, including humans, β-adrenoceptors have been shown to dominate over α-adrenoceptors, and the normal response to released norepinephrine is relaxation.[42,43]

α-Adrenoceptors. The predominating postjunctional α-adrenoceptor subtype in the human LUT seems to be α_1.[44,45] Recently, Walden *et al.*[45] reported a predominance of α_{1a}-adrenoceptor protein in the human bladder dome, trigone, and bladder base, but which α_1-adrenoceptor subtype predominates functionally has not been clarified. Possibly, the α_{1L}-adrenoceptor subtype is the one mediating contractile responses.[46]

Drugs stimulating α-adrenoceptors have hardly any contractile effects in isolated, normal human detrusor muscle. However, even if the α-adrenoceptors have no significant role in normal bladder contraction, there is evidence that this may change in bladder overactivity associated with, for example, outflow obstruction, neurogenic bladders, and idiopathic bladder instability.

Perlberg and Caine[42] found that norepinephrine caused contraction instead of the normal relaxant response in bladder strips from 11 of 47 patients with benign prostatic obstruction. They proposed that there was a correlation between the response to stimulation on one hand, and bladder instability and irritative symptoms on the other. It has been observed that in patients with BPH treated with α-adrenoceptor blockers, bladder overactivity (bladder instability) disappears during treatment.[47] Taken together, these observations would suggest that there may be an increased α-adrenoceptor function associated with the morphologic changes occurring in bladder hypertrophy. On the other hand, Smith and Chapple[48] could not confirm the occurrence of an increased α-adrenoceptor function in the unstable, obstructed human bladder.

A change in the α-adrenoceptor function of the detrusor and outflow region associated with outflow obstruction secondary to BPH cannot be excluded. On the other hand, the importance of such a change for the clinical response to α-adrenoceptor antagonists is difficult to assess. It cannot be excluded that an effect of the α-adrenoceptor blockers on the CNS contributed to these actions. There are clinical observations in agreement with the view that neurologic damage may be associated with a change in α-adrenoceptor functions of relevance to detrusor function. In a study of patients with bladder hyperreflexia, Jensen[49] found that treatment with prazosin decreased the overactivity and increased bladder capacity. This was confirmed by other investigators,[50] but the results were not impressive. In children with myelomeningocele and detrusor hyperreflexia, phentolamine injected intramuscularly decreased tone and bladder overactivity.[51] Detrusor tissue from patients with bladder overactivity (without neurologic disorders) had an almost fourfold increase in the density of α-adrenoceptors compared to the density in patients with normal bladder activity.[40] The importance of this finding for bladder overactivity is, however, unclear.

The α_1-adrenoceptor subtypes of the LUT and those involved in the central control of the micturition reflexes deserve further attention. Whether or not drugs with a selective effect on α_{1L}-adrenoceptors can eliminate bladder overactivity should be investigated.

β-Adrenoceptors. In isolated human bladder, non–subtype-selective and β-adrenoceptor agonists, such as isoprenaline, have a pronounced inhibitory effect.[2] It was speculated that, in bladder overactivity, there is a lack of an inhibitory β-adrenoceptor-mediated norepinephrine response. However, detrusor muscle from patients with bladder instability was reported to show a similar degree of inhibition in response to isoprenaline as normal detrusor,[52] even if the inhibitory effect of isoprenaline on the response to electrical stimulation was less in unstable muscle. However, the β-adrenoceptors of the human bladder were shown

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