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CNS Involvement in Overactive Bladder

Pathophysiology and Opportunities for Pharmacological Intervention

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Abstract

The pathophysiology of overactive bladder (OAB) syndrome is complex, and involves both peripheral and CNS factors. Several CNS disorders are associated with OAB, e.g. stroke, spinal cord injury, Parkinson's disease and multiple sclerosis, and in each disorder the pathophysiology of OAB can be multifactorial. Irrespective of cause or pathophysiology of OAB, antimuscarinic drugs are the first line of pharmacological treatment. However, adverse effects and limited efficacy makes alternative therapeutic principles desirable. Most alternative drugs used for the treatment of OAB have a peripheral site of action, mainly affecting efferent or afferent neurotransmission or the detrusor muscle itself. New targets for pharmacological intervention may be found in the CNS.

Several CNS transmitters/transmitter systems are known to be involved in micturition control, but few drugs with a defined CNS site of action (e.g. baclofen, imipramine and duloxetine) have been used for the treatment of voiding disorders.

GABA, glutamate, opioid, serotonin, noradrenaline (norepinephrine), and dopamine receptors and mechanisms are known to influence micturition, and drugs influencing these systems could potentially be developed for the treatment of OAB.

Preclinical studies in different animal models have shown that modulation of normal micturition and detrusor overactivity by drugs acting within the spinal cord or supraspinally is possible. Promising results have been obtained in such models, e.g. with drugs interfering with GABA mechanisms, serotonin 5-HT_{1A} receptors, μ-opioid receptors and α-adrenoreceptors. However, considering the limited predictability of existing animal models for efficacy in humans, positive proof of concept studies in humans are mandatory. Such studies are scarce and further investigations are needed.

Overactive bladder (OAB) is a syndrome comprising urgency, with or without urinary incontinence, and usually with increased voiding frequency and nocturia.[1] OAB may have many causes and several pathophysiological mechanisms can be involved both centrally and peripherally.[2] It should be underlined that OAB is a symptom diagnosis. Although often caused by detrusor overactivity, it is not synonymous with this condition, which is diagnosed by urodynamic investigation.

Most drugs currently used to treat OAB act peripherally and may be classified as drugs whose major action is to reduce detrusor contractility (directly or indirectly) and drugs that affect afferent bladder nerves. Antimuscarinic agents are still first-line pharmacological therapy.[3] These drugs reduce urge, stabilise detrusor overactivity and increase bladder capacity. While they are undeniably clinically efficacious, their clinical use is limited by the well known adverse effects of dry mouth, blurred vision, constipation, and sometimes somnolence and impaired cognitive functions. Drugs acting through other mechanisms have also been found to be efficacious, including intravesical capsaicin and resiniferatoxin, which affect sensory nerves and block the afferent limb of the micturition reflex.[3] However, capsaicin may cause pain on instillation and resiniferatoxin is, in practice, difficult to handle.

The adverse effects of the antimuscarinic drugs, and the limitations of capsaicin and resiniferatoxin, have focused interest on alternative treatment targets. Such targets may be found in the CNS but, despite promising effects in animal models, few new treatment principles have been documented to be clinically efficacious in OAB.[4] In this article, the pathophysiological aspects of some CNS diseases often associated with OAB and detrusor overactivity are briefly reviewed, and possible targets for therapeutic interventions are discussed.

1. Nervous Control of Micturition

Normal micturition in both humans and animals occurs in response to afferent signals from the lower urinary tract (LUT), and is controlled by neural circuits in the brain and spinal cord (figure 1 and figure 2).[5-7] These circuits co-ordinate the activity of the smooth muscle in the detrusor and urethra with that of the striated muscle in the urethral sphincter and pelvic floor. Pontine influences are believed to act as on-off switches to shift the LUT between two modes of operation: storage and voiding.[8] In adults, urine storage and voiding are subject to voluntary control, but in infants these switching mechanisms function in a reflex manner to produce involuntary voiding.[8] Injuries or diseases of the CNS in adults can disrupt the voluntary control of micturition and cause the re-emergence of reflex micturition, resulting in OAB, detrusor overactivity and urinary incontinence. Because of the complexity of the CNS control of the LUT, OAB and detrusor overactivity can occur as a result of a variety of neurological disorders, as well as changes in the

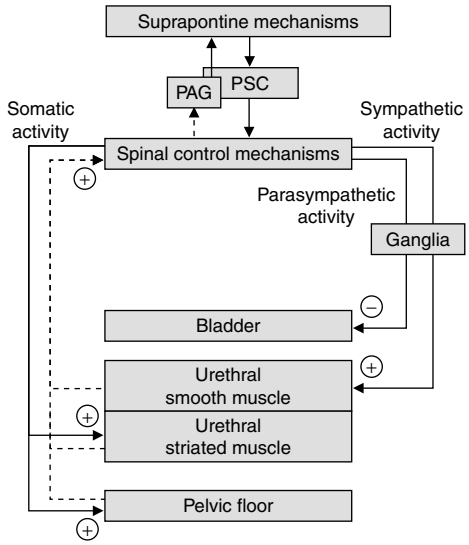

Fig. 1. Storage reflexes. During filling, there is continuous and increasing afferent activity from the bladder. There is no spinal parasympathetic outflow that can contract the bladder. The sympathetic outflow to the urethral smooth muscle and the somatic outflow to urethral and pelvic floor-striated muscles keep the outflow region closed. Whether or not the sympathetic innervation to the bladder (not indicated) contributes to bladder relaxation during filling in humans has not been established. **PAG** = periaqueductal grey; **PSC** = pontine urine storage centre.

peripheral innervation and smooth and skeletal muscle components.[5]

Distension of the bladder wall is considered the primary stimulus for initiation of the micturition reflex. In addition, mechanisms related to the urothelium and adjacent afferent nerves may serve as volume sensors.[9] At least two types of afferent neurons innervate the urinary bladder. One type (Aδ) is mechanosensitive, with myelinated axons, and is activated by both low (non-nociceptive) and high (nociceptive) intravesical pressures. The second type of afferents (C-fibres) do not respond to bladder distension, possess unmyelinated axons and are activated by cold, heat or chemical irritation of the bladder mucosa. These latter afferents are believed to have primarily nociceptive functions,[10] but also to contribute to micturition in the foetus, neonatally and when the bladder and/or the micturition reflex is damaged in adult life.

During bladder filling, once threshold tension is achieved, afferent impulses conveyed mainly by the pelvic nerve reach centres in the CNS. The afferent neurons send information to the periaqueductal grey (PAG), which in turn communicates with the pontine tegmentum,[11] where two different regions involved in micturition control have been described.[12,13] One is a dorsomedially located M region, corresponding to Barrington's nucleus or the pontine micturition centre (PMC). A more laterally located L-region may serve as a pontine urine storage centre (PSC), which has been suggested to suppress bladder contraction and to regulate the striated urethral sphincter muscle activity during urine storage. The M- and L-regions may represent separate functional systems acting independently.[14]

The suprapontine control of PMC and PSC has not been clarified in detail;[15] several positron emission tomography studies have been performed in humans and suggest involvement of a number of structures, including the inferior frontal gyrus and the anterior cingulate gyrus.[16-18] Descending pathways connect with preganglionic neurones originating in the lumbar sympathetic and sacral parasympathetic nuclei, and with somatic motoneurons innervating the striated urethral sphincter (Onuf's nucleus). The co-ordination between the detrusor and the sphincter occurs in the pontine region, implying that injuries below this region may be associated with detrusor-sphincter dyssynergia.[19]

2. CNS Disorders and Overactive Bladder Syndrome

The complexity of the central control of micturition implies that both localised and more generalised changes within the CNS may lead to voiding disturbances, including OAB. A common reason for incontinence in the elderly is dementia, but the defect in cognitive function is not necessarily responsible for the lack of continence in these patients.[19] Other common disorders associated with the OAB syndrome include stroke, spinal cord injury, Parkinson's disease and multiple sclerosis.[15]

2.1 Stroke

Cerebrovascular accidents are frequently associated with urinary symptoms and the likelihood of

early poststroke incontinence is 57–83%.[20] In patients with various cortical lesions, voiding is generally co-ordinated and there is no detrusor-sphincter dyssynergia. Thus, urinary incontinence results from uninhibited detrusor contractions as a result of damage to the cerebral inhibitory centres. In acute stroke, urinary incontinence seems to be a powerful indicator for poor survival.[20]

Sakakibara et al.[21] suggested that damage to the anteromedial frontal lobe, its descending pathways and the basal ganglia was mainly responsible for micturition dysfunction in stroke patients. The predominant symptoms are urinary frequency, urgency and urge incontinence. Urodynamically, the most common finding is neurogenic detrusor overactivity, i.e. detrusor overactivity "when there is a relevant neurological condition".[1] Interestingly, in the majority of patients after stroke, electromyography reveals uninhibited relaxation of the external sphincter during or preceding detrusor contractions, with resultant urinary incontinence.[20]

Animal models of stroke have provided some insights into the pathophysiological mechanisms involved in the development of stroke-associated OAB. Experimental cerebral infarction after occlusion of the middle cerebral artery in rats produces ischaemia within the putamen and cortex,[22] areas of importance for micturition. Detrusor overactivity, characterised by an increased micturition frequency and decreased bladder capacity, can be observed in these rats as soon as 30 minutes after infarction.[23,24] This supports the notion of tonic cortical inhibition of bladder function.

Yokoyama et al.[25] proposed that the decrease in bladder capacity associated with cerebral infarction was due to upregulation of an excitatory pathway from the forebrain and downregulation of a tonic inhibitory pathway from the same region. This overactivity might involve NMDA glutamatergic mechanisms since it was reversed by an NMDA receptor antagonist. Also, dopamine D_2 receptor excitatory mechanisms seemed to be implicated since sulpiride, selectively blocking D_2-like receptors, increased bladder capacity in rats with cerebral infarction.[26] Other factors involved may be alterations in dopaminergic-glutamatergic interactions in the brain,[27] a central mechanism sensitive to nitric oxide[28] and a decreased GABA-mediated inhibition of micturition.[29]

2.2 Spinal Cord Injury

In spinal cord injury, the degree of urinary dysfunction is related to the disease process itself, the area of the spinal cord affected by the disease and the severity of neurological impairment.[7,15] Neurological injury can involve parasympathetic, sympathetic and somatic nerve fibres, and can result in a complex combination of signs and symptoms.

Overactive urinary voiding develops days to weeks after acute spinal cord injury. Damage to the spinal cord above the sacral level results in detrusor overactivity. This type of neurogenic detrusor overactivity is associated with the emergence of a capsaicin-sensitive C-fibre-mediated spinal micturition reflex caused by a reorganisation of synaptic connections in the spinal cord. In addition, bladder afferents that are normally unresponsive to low in-

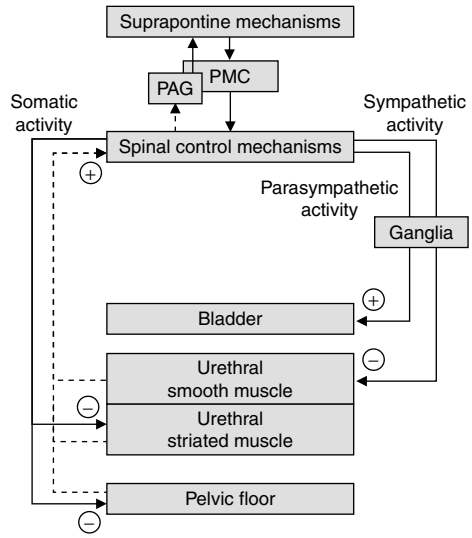

Fig. 2. Voiding reflexes involve supraspinal pathways and are under voluntary control (except in infants). During bladder emptying, the spinal parasympathetic outflow is activated, leading to bladder contraction. Simultaneously, the sympathetic outflow to the urethral smooth muscle and the somatic outflow to urethral and pelvic floor-striated muscles are turned off, and the outflow region relaxes. **PAG** = periaqueductal grey; **PMC** = pontine micturition centre.

travesical pressures become more mechanosensitive, leading to the development of detrusor overactivity.[5] As mentioned previously, normal micturition is associated with a spinobulbar-spinal reflex mediated by lightly myelinated Aδ afferents. In the cat, most C-fibres remain silent during normal filling of the bladder, but in the rat, some studies indicate that C-fibres can fire at low pressures; other studies showed firing at high intravesical pressures (approximately 30mm Hg).[5] These C-fibre afferents are thought to play a role in the development of detrusor overactivity after spinal cord injury. Capsaicin sensitive C-fibres have also been implicated in detrusor overactivity following upper motor neuron diseases such as multiple sclerosis and Parkinson's disease.

A mechanism underlying the increased mechanosensitivity of C-fibres after spinal cord injury may be plasticity of the dorsal root ganglion cells supplying the bladder. This is manifested by enlargement of these cells and increased electrical excitability. A shift in the expression of Na^+ channels from a high threshold tetrodotoxin (TTX)-resistant type to a low threshold TTX-sensitive type is known to occur after spinal cord injury.[5]

2.3 Parkinson's Disease

Parkinson's disease is one of the most common neurological entities causing voiding dysfunction, often resulting in detrusor overactivity and an impairment of relaxation of the striated urethral sphincter.[30] Urinary symptoms are primarily of storage type (frequency, urgency, urge incontinence) and correlate with the urodynamic finding of involuntary detrusor contractions at early stages of bladder filling. Detrusor overactivity increases with progression and severity of the disease and can be found in up to 90% of patients in the later stages of the disease.[15,19,31] Voiding (obstructive) symptoms, such as hesitancy and weak urinary stream, may be seen in a smaller number of patients, often combined with storage symptoms. In men, part of this symptomatology may be attributed to co-existing benign prostatic hyperplasia (BPH). The reported prevalence of dysfunction of the striated urethral sphincter and pelvic musculature in patients with Parkinson's disease is variable; when dysfunction is present, the main abnormality is that of delayed relaxation at the time of initiation of voluntary voiding.

The majority (>70%) of female patients with Parkinson's disease who also have urinary symptoms will manifest symptomatic urgency with or without urge incontinence.[32] The remaining affected patients will have mixed storage and voiding, or purely voiding symptoms.

It has been suggested that, normally, the basal ganglia have an inhibitory effect on the micturition reflex and that cell loss in the substantia nigra will lead to detrusor overactivity. Experimental data in cats and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys have suggested that D_1-like (D_1 and D_5) receptors exert an inhibitory influence on the micturition reflex.[33,34] On the basis of experiments in conscious rats, Seki et al.[35] suggested that D_1-like receptors tonically inhibit and that D_2-like (D_{2A}, D_{2B}, D_3 and D_4) receptors are involved in facilitation of the micturition reflex. They speculated that neurogenic detrusor overactivity associated with Parkinson's disease results from activation failure of D_1 receptors.

2.4 Multiple Sclerosis

In multiple sclerosis, voiding dysfunction is mainly due to spinal lesions, although cerebral lesions may contribute. Impairment of neurological function results from demyelinating plaques of the white matter of the brain and spinal cord, especially the posterior and lateral columns of the cervical cord. This means that depending on the site of lesions, different pathophysiological mechanisms may be involved in the OAB of patients with multiple sclerosis.[36,37]

Symptoms of voiding dysfunction can be found in 90% of patients having had multiple sclerosis for >10 years. These symptoms not only include frequency, urgency and urge incontinence, but also urinary hesitancy, intermittency and poor urinary stream.[37] Urodynamically, the most common pattern seen is neurogenic detrusor overactivity (in

about 70% of affected patients), and this is accompanied by detrusor-external sphincter dyssynergia in about 50% of patients.[38]

Animal models analogous to bladder dysfunction in multiple sclerosis are available[39] but experiences of experimental therapeutic interventions seem to be lacking.

3. Targets for Pharmacological Intervention

The micturition reflexes involve several neurotransmitters and transmitter systems that may be targets for drugs aimed at control of micturition. Glutamate is probably involved as an excitatory transmitter in the supraspinal control circuitry and also in the efferent limb of the pathway between the PMC and the preganglionic neuron.[40,41] Antagonists of glutamic acid receptors in rats with experimental cerebral infarction were effective in abolishing stroke-mediated detrusor overactivity.[23,26] However, the involvement of glutamate in many CNS functions may be a limiting factor for the development of drugs specifically targeting OAB. Several other substances can exert modulatory effects on the glutamatergic mechanisms controlling micturition, and the receptors for these substances may represent potential sites for therapeutic interventions. Among such substances are GABA, serotonin, dopamine and noradrenaline (norepinephrine).

4. GABA

GABA has been identified as an inhibitory neurotransmitter at both spinal and supraspinal synapses in the mammalian CNS and, at least in some species, the supraspinal micturition reflex pathway is under a tonic GABAergic inhibitory control.[5,8] The highly flexible GABA molecule acts on three different GABA receptor types: $GABA_A$, $GABA_B$ and $GABA_C$.[42] Both $GABA_A$ and $GABA_B$ receptors are present in the brain[43,44] and in the spinal cord. However, in the spinal cord $GABA_A$ receptors are more numerous than $GABA_B$ receptors, except for the dorsal horn where $GABA_B$ receptors predominate.[45,46]

GABA transporters, present on neuronal and glial cells in the brain, brainstem and spinal cord,[47] are presumed to provide an inactivation mechanism.[46] Four different GABA transporters (GATs) have been described.[43] Tiagabine is a selective inhibitor of one of these GABA transporters, named GAT1,[48] and is able to increase extracellular levels of GABA.[49]

Therefore, not only GABA receptors but also mechanisms controlling reuptake or breakdown of GABA can be targets for pharmacological intervention.

GABA-containing interneurons are inhibitory for both spinal bladder efferents[41] and in the brain.[50,51] Since blockade of $GABA_A$ and $GABA_B$ receptors in the spinal cord[52,53] and brain[50,53] stimulated rat micturition, an endogenous activation of $GABA_{A+B}$ receptors may be responsible for continuous inhibition of the micturition reflex within the CNS. Experiments using conscious and anaesthetised rats have demonstrated that this action can be reinforced; micturition is inhibited by exogenous GABA, the $GABA_A$ receptor agonist muscimol and the $GABA_B$ receptor agonist baclofen given intravenously, intrathecally or intracerebroventricularly.[29,50,53-56] Similar effects were obtained in awake mice.[57] Also, inhibition of GABA breakdown[50] and inhibition of GABA reuptake[58] are inhibitory for rat micturition. In mice, where detrusor overactivity was produced by intravesical citric acid, subcutaneous baclofen had an inhibitory effect that was blocked by the selective $GABA_B$ receptor antagonist CGP-55845.[57]

Stimulation of the PMC results in an immediate relaxation of the external striated sphincter and a contraction of the detrusor muscle of the bladder. The motor neurons of Onuf's nucleus project to the striated urethral sphincter and cause contraction. Blok et al.[59] demonstrated in cats a direct pathway from the PMC to the dorsal grey commissure of the sacral cord. More than half (55%) of these terminals made contact with GABA immunoreactive neurons. It was suggested that the pathway produced relaxation of the external striated sphincter during micturition via inhibitory modulation by GABA neurons of

the motoneurons in the nucleus of Onuf.[59] Thus, intrathecal baclofen and muscimol ultimately produced dribbling urinary incontinence.[52,53] Given the effects of spinal $GABA_A$ and $GABA_B$ receptor blockade as well as GABA reuptake inhibition, normal relaxation of the striated urethral sphincter is probably mediated via $GABA_A$ receptors.[52,53,58] Supporting this, Zhu et al.[57] found that in conscious mice, muscimol and diazepam caused dribbling incontinence, probably via an effect on Onuf's nucleus.

$GABA_B$ receptors have a minor influence on motoneuron excitability.[60] However, intrathecal baclofen attenuated oxyhaemoglobin-induced detrusor overactivity, suggesting that the inhibitory actions of $GABA_B$ receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fibre activation in the urothelium and/or suburothelium.[53]

GABA may act as an inhibitory neurotransmitter in the brain and depress excitatory (diencephalon) or inhibitory (mesencephalon and telencephalon) mechanisms for micturition control. Thus, GABA injected into different areas of the pons in cats may decrease or increase bladder capacity, depending on its interaction with brainstem centres involved in either storage or voiding.[61] Low doses of intracerebroventricular muscimol and baclofen were without effects in normal conscious rats, but decreased bladder capacity in rats with cerebral infarction, i.e. with damage to areas likely to be inhibitory for micturition.[25] High doses of muscimol and baclofen increased bladder capacity, eventually leading to dribbling incontinence in both normal and cerebral infarct rats. Hence, the effect of GABA receptor activation on micturition may differ between various brain areas. The effect of $GABA_B$ receptor activation at concentrations that may be reached after intravenous tiagabine, for example, may have dual effects on micturition related to inhibition of brain centres with inhibitory or excitatory effects on bladder function.[58]

4.1 Therapeutic Effects and Opportunities

Baclofen has been used in voiding disorders, including neurogenic detrusor overactivity (detrusor hyperreflexia) secondary to lesions of the spinal cord. In patients with bladder dysfunction associated with spasticity, intrathecal baclofen attenuated symptoms of detrusor sphincter dyssynergia and autonomic dysreflexia.[62,63] Some of these patients had not tolerated oral baclofen, a treatment claimed to be effective against idiopathic detrusor overactivity.[64] However, despite a high incidence of intolerable adverse effects, oral baclofen was effective against detrusor-sphincter dyssynergia.[65,66] Interaction with GABA receptors is an effective way to influence micturition control; however, baclofen may not be an ideal drug to treat detrusor overactivity and OAB.

Examples of possible GABA-mediated therapeutic strategies include:

- the use of selective $GABA_B$ receptor agonists penetrating the blood-brain barrier;
- inhibition of either breakdown or reuptake of GABA; and
- use of allosteric modulators of GABA receptors.

Diazepam is an allosteric modulator of the $GABA_A$ receptors, and it suppresses isovolumetric bladder contractions and abolishes micturition in anaesthetised rats[50,54] and mice.[57] Since the well known adverse effects of diazepam limit its use, other allosteric modulators may be of interest. Further exploration of the possibilities of the extraordinary structural diversity of the $GABA_A$ receptor[44] may also offer a useful approach.

5. Serotonin

The lumbosacral autonomic nuclei, as well as the somatic motor nuclei (Onuf's nuclei), receive a dense serotonergic input from the raphe nuclei, and multiple serotonin 5-HT receptors have been found at sites where processing of afferent and efferent impulses from and to the LUT take place.[67-71] Depending on the predominant receptor subtype at the site of action, serotonin may either inhibit or facilitate micturition when given experimentally. How-

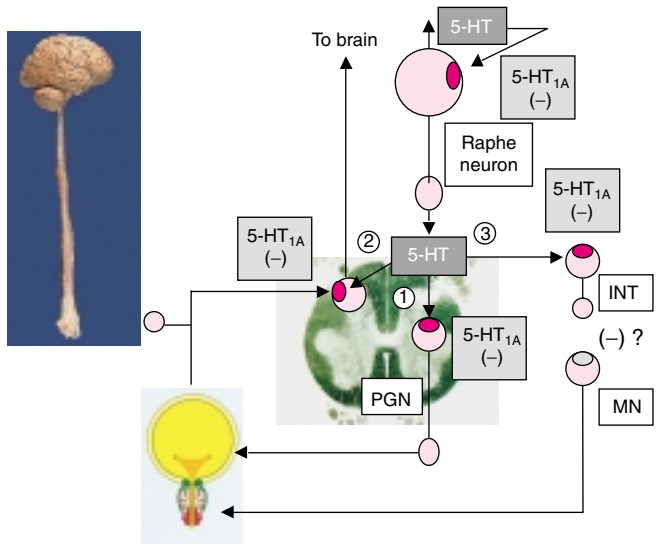

Fig. 3. A model for the effects of serotonin on the lower urinary tract. The raphe neurons release serotonin (5-HT) at several lumbosacral levels. Lower urinary tract activity is influenced via inhibitory serotonin 5-HT_{1A} receptors on: (**1**) preganglionic parasympathetic neurons (PGN); (**2**) neurons conveying afferent information to the brain; and (**3**) interneurons (INT) providing inhibitory input to the motoneurons (MN) to the striated urethral sphincter. The raphe neurons are endowed with inhibitory 5-HT_{1A} autoreceptors. Blockade of these receptors would increase firing in the raphe neurons and enhance the spinal inhibitory effect of serotonin on the bladder, but possibly produce increased activity in the MN to the striated sphincter (loss of inhibitory input). The receptor on the MN is not known (indicated by ? in the figure).[77]

ever, the descending pathway is essentially an inhibitory circuit, with serotonin as a key neurotransmitter.[8] Thus, electrical stimulation of serotonin-containing neurons in the caudal raphe nucleus causes inhibition of bladder contractions.[72,73]

The serotonin receptors have been divided into seven families (5-HT_{1-7}) on the basis of sequence homology, pharmacology and signalling pathways.[74] They comprise a large number of receptors, many of which exhibit distinct pharmacological profiles.[75] All of these receptors, except the 5-HT_3 receptors that are ligand-gated ion channels,[75,76] are G-protein coupled, predominantly inhibiting adenylate cyclase via G_i/G_o G proteins. The 5-HT_{1A} receptor, which is currently receiving attention because of its effects on LUT functions, can also couple to alternative signalling cascades (stimulating K^+ channels, activating mitogen-activated protein kinase), although the physiological significance of these signalling pathways are, at present, poorly understood.

de Groat[77] proposed a model for explaining the effects of serotonin on the LUT (figure 3).

However, the effects of serotonin and of receptor subtype-selective agonists and antagonists are complicated and differ between species.[77] Thus, in anaesthetised cats, intrathecal serotonin increased micturition volume, and blockade of spinal 5-HT_3[78,79] and 5-HT_2[80] receptors decreased bladder capacity. In rats, intrathecal serotonin and selective stimulation of spinal 5-HT_{1A} receptors facilitated micturition.[80,81] Ishizuka et al.[82] found that in normal conscious rats, intracerebroventricular serotonin (via 5-HT_{1A}, 5-HT_2 and 5-HT_4 receptors) enhanced the micturition reflex induced by bladder filling. On the other hand, Testa et al.[83] showed that antagonists of 5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_6 receptor subtypes were poorly active or inactive in a model of isovolumetric detrusor contraction in rats. Similarly, these compounds were inactive on cystometry in conscious animals. In contrast, blockade of 5-HT_{1A} receptors by neutral antagonists (i.e. antagonists lacking effects of their own) in conscious

rats inhibited micturition.[81,84] Spinal 5-HT_{1A} receptor blockade by the selective antagonist WAY-100635 inhibited isovolumetric bladder contractions in urethane-anaesthetised rats.[85] However, similar doses were ineffective in conscious rats,[81] casting doubts about the importance of spinal 5-HT_{1A} receptors for serotonin-induced inhibition of micturition. Blockade of 5-HT_2 receptors was found to facilitate rat micturition[83] and tended to increase the frequency of isovolumetric bladder contractions.[84] Spinal 5-HT_2 receptors may, therefore, be the serotonin receptor subtype mediating not only the inhibitory action of 5-HT_2 receptor agonists but also responsible for endogenous serotonin-mediated spinal inhibition of micturition in rats.

The nucleus of Onuf, which innervates the urethral striated muscle sphincter, has a dense serotonergic innervation (monkeys[86]) and a high density of 5-HT_{1A} receptors (rats[70]). A major effect of the serotonergic system originating in the raphe nuclei is to enhance spinal motoneuron excitability.[60] Thus, in anaesthetised cats, the 5-HT_{1A} receptor agonist 8-OH-DPAT increased sphincter electromyographic (EMG) activity.[87] In conscious rats, 8-OH-DPAT increased micturition pressure but spinal 5-HT_{1A} receptor blockade did not decrease micturition pressure, suggesting that there is no tonic activation via these receptors.[81]

5.1 Therapeutic Effects and Opportunities

Stimulation by serotonin, and especially selective stimulation of 5-HT_{1A} receptors, in the rat brain facilitated micturition by a mechanism sensitive for serotonin depletion, thus presumably acting via spinal descending neurons.[80-82] Since blockade of brain 5-HT_{1A} receptors inhibited micturition,[81] these receptors (rather than spinal 5-HT_{1A} receptors) may represent a possible target for micturition control in OAB. Indeed, 5-HT_{1A} receptor blockade counteracted detrusor overactivity resulting from experimental C-fibre stimulation in rats.[88]

Rats depleted of serotonin show detrusor overactivity.[89] Hence, drugs interfering with serotonin reuptake, for example the selective serotonin reuptake inhibitors (SSRI), may have the opposite effects. The tricyclic agent imipramine, which inhibits the reuptake of both serotonin and noradrenaline, depressed rat bladder activity by a serotonin depletion-sensitive mechanism in anaesthetised rats.[90] Citalopram, an SSRI, did not alter isovolumetric bladder contractions in rats.[84] Nevertheless, in cats, duloxetine and venlafaxine (inhibitors of serotonin and noradrenaline reuptake) increased sphincter EMG activity and bladder capacity.[91,92] Promising clinical experiences with duloxetine in the treatment of stress incontinence have been reported.[93] However, no systematic testing of SSRIs as a treatment for detrusor overactivity in humans has been performed. Interestingly, the use of SSRIs may be associated with an increased risk of developing urinary incontinence.[94]

The serotonin system undoubtedly has an important influence on micturition in several animal models. Even if available data from such studies suggest that 5-HT receptors and reuptake mechanisms for serotonin are interesting targets for drugs meant for treatment of OAB, it is difficult to assess their relevance for humans. Until proof-of-concept studies have been performed with 5-HT_{1A} antagonists and selective SSRIs, the potential value of these principles remains speculative.

6. Enkephalins

Endogenous opioid peptides and corresponding receptors are widely distributed within the brain. Precursors for opioid peptides, as well as areas with dense opioid binding, are found in many regions in the neuroaxis, including areas of importance for micturition control, e.g. PAG, PMC, spinal parasympathetic nucleus and the nucleus of Onuf.[41,95,96]

At least three different opioid receptors – μ, δ and κ – bind stereospecifically with morphine and have been shown to interfere with urinary voiding mechanisms. Morphine increased bladder capacity or blocked isovolumetric bladder contractions when given intravenously, intraperitoneally or intrathecally to conscious rats,[97-99] dogs[100] and humans,[101] or intravenously, intrathecally or intracerebroventricularly to anaesthetised rats[102-107] and dogs.[107] Furthermore, naloxone – a μ-opioid receptor ant-

agonist – stimulated micturition when given intrathecally to anaesthetised rats and intravenously to humans.[108,109] This suggests that μ receptors exert a tonic inhibitory control of the micturition reflex. However, intrathecal naloxone was not effective in stimulating micturition in conscious rats at doses blocking the effects of intrathecal morphine.[97,98]

Stimulation of intracerebroventricular and intrathecal δ-opioid receptors in anaesthetised cats and rats inhibited micturition[110,111] and inhibited parasympathetic neurotransmission in cat bladder ganglia.[112] Also interference with σ-opioid receptors has been shown to have effects on micturition, with stimulation of σ-opioid receptors blocking isovolumetric bladder contractions in anaesthetised rats.[113,114] In humans, nalbuphine, a μ-receptor antagonist and κ-receptor agonist, increased bladder capacity.[101]

6.1 Therapeutic Effects and Opportunities

Intrathecal morphine was shown to be effective in patients with detrusor overactivity caused by spinal cord lesions,[115] but was associated with adverse effects such as nausea and pruritus. Further adverse effects of traditional opioid receptor agonists include respiratory depression, constipation and the potential for abuse of the drug. Drug research has tried to limit these adverse effects by increasing selectivity towards one of the different opioid receptor types.[116]

The analgesic drug tramadol combines weak effects on opioid receptors with reuptake inhibition of serotonin and noradrenaline,[117] and for moderate pain the drug is as effective as morphine but with fewer adverse effects.[118] Tramadol inhibits micturition in conscious rats, at doses below those resulting in analgesia.[99] The dose range resulting in inhibition of micturition, but not dribbling incontinence, is much wider than that for morphine, even though its main mechanism is μ-opioid receptor stimulation.[99] Tramadol abolishes experimentally induced detrusor overactivity caused by dopamine receptor activation[119] or cerebral infarction in rats.[120] These data suggest that tramadol may have a clinically useful effect on detrusor overactivity.

Although morphine did not increase micturition pressure in humans, buprenorphine (a partial μ-receptor agonist and κ-receptor antagonist) decreased micturition pressure and increased bladder capacity.[101] These results suggest that other effects besides μ-opioid receptor stimulation, perhaps κ-receptor stimulation, might explain why tramadol was more effective in increasing bladder capacity, and was much less likely to abolish effective micturitions, than morphine.[99] Further exploration of these non-μ-opioid receptor-mediated actions on micturition seem warranted.

7. Dopamine

As mentioned previously, central dopaminergic pathways have both excitatory and inhibitory effects on rat bladder function.[41] In the normal rat, activation of D_1-like receptors inhibits micturition and activation of D_2-like receptors stimulates micturition. Blockade of D_1-like receptors stimulates micturition, whereas blockade of D_2-like receptors has no effect on micturition in the rat.[26,35,121] Hence, D_1-like receptors may tonically inhibit the micturition reflex and D_2-like receptors are involved in its facilitation.

Dopamine receptors are found in the brain[122] and spinal cord,[123] as well as in the pelvic ganglion where dopamine inhibits ganglionic transmission.[8] In pontine nuclei, messenger RNA (mRNA) for D_2-like, but not D_1-like, receptors has been found.[122,124] In the spinal cord, D_2-like receptors have the highest density in the dorsal horn and in the parasympathetic area in the sacral spinal cord segment.[123]

Local injection of dopamine into the cat PMC stimulated micturition via D_2-like receptors,[41] as did intrathecal apomorphine (stimulating both D_1- and D_2-like receptors) when administered to anaesthetised rats.[121] In the brain, D_1-like receptors are more common than D_2-like receptors,[122] and mRNA for D_1-like receptors has a relatively higher expression in the telencephalon than observed for D_2-like receptor mRNA.[124]

As mentioned in section 2.3, patients with idiopathic Parkinson's disease, characterised by selec-

tive destruction of striatal (nucleus caudatus and putamen) dopaminergic neurons that pass from substantia nigra pars compacta to the putamen, exhibit detrusor overactivity.[125-127] Similarly, detrusor overactivity is seen in monkeys in whom dopamine has been depleted from the striatum after exposure to a neurotoxin (MPTP) selective for the substantia nigra.[33,34] The loss of inhibitory D_1-like receptors has been suggested to be the mechanism behind the detrusor overactivity, at least in parkinsonian monkeys,[34] allowing D_2-like receptors to facilitate micturition.

7.1 Therapeutic Effects and Opportunities

Levodopa, a dopamine precursor, is currently the most effective drug for treatment of parkinsonian symptoms. L-dopa stimulates both D_1- and D_2-like receptors,[128] but has been reported to worsen neurogenic detrusor overactivity and decrease bladder capacity.[129] Other dopaminergic drugs such as apomorphine,[130] BAM-1110 and pergolide,[131] although also stimulating both D_1- and D_2-like receptors, seem to improve bladder dysfunction in patients with Parkinson's disease and parkinsonian monkeys, probably via stimulation of D_1-like receptors.[34,131]

The effects of highly selective D_1-like receptor agonists, and of antagonists selectively acting at D_{2A}, D_{2B}, D_3 or D_4 receptors, have not been established. Further studies on such selective dopamine receptor agents seem warranted.

Both decerebration and cerebral infarction may uncover a tonic activation of D_2-like receptors distal to supracollicular cleavage, i.e. the hypothalamus, brainstem and spinal cord.[25,26] Experimental cerebral infarction yields damage to the basal ganglia and motor cortex,[22] which may be areas suppressing D_2-like receptor-mediated actions in the normal rat. Antagonism of D_2-like receptors had no effect on bladder capacity in normal conscious rats, but increased bladder capacity in cerebral infarcted rats.[26] Thus, selective blockade of D_2-like receptors, or a specific D_2-like receptor, could be helpful in stroke patients with OAB.

8. Noradrenaline (Norepinephrine)

Neurons in the locus coeruleus react to bladder filling,[132] and noradrenergic neurons originating in this region project to the autonomic and somatic nuclei in the lumbosacral spinal cord. Although destruction of the noradrenergic pathways with 6-*OH*-dopamine did not change micturition in rats, there is ample evidence that bulbospinal noradrenergic pathways are involved in the supraspinal control of micturition.[8]

Both α_1-and α_2-adrenoceptors seem to be involved in micturition control. Smith et al.[133] performed *in situ* hybridisation to identify cell bodies containing α_1-adrenoceptor subtype mRNA at four levels of human spinal cord (cervical enlargement, thoracic, lumbar and sacral). α_1-Adrenoceptor mRNA was present in grey matter only, particularly in the sacral region (the spinal parasympathetic nucleus). Although all three α_1-adrenoceptor subtypes were present throughout the human spinal cord, α_{1D}-adrenoceptor mRNA predominated overall.

Facilitatory α_1-adrenoceptors seem to be tonically active in both the sympathetic and somatic neural control of the LUT.[134,135] Ishizuka et al.[136] and Gu et al.[137] gave intrathecal and intracerebroventricular α_1-adrenoceptor antagonists, respectively, to normal rats and rats with outflow obstruction. Intrathecal doxazosin decreased micturition pressure, both in normal rats and in animals with post-obstruction bladder hypertrophy/overactivity,[136] the effect being much more pronounced in the animals with obstructed bladders. Doxazosin did not markedly affect the frequency or amplitude of the non-voiding contractions observed in the rats with outflow obstruction. Intracerebroventricular prazosin and terazosin significantly decreased voiding pressure and increased bladder capacity, voided volume and post-void residual urine volume.[137] The α_{1A}-adrenoceptor subtype seemed to mediate the effect. The drug effects were significantly more pronounced in rats with outlet obstruction than in normal animals, and urinary retention was produced in 50% of rats receiving prazosin. These results suggest that volume-induced bladder activity involves both supraspinal and spinal α_1-adrenoceptors. Blad-

der outlet obstruction seems to enhance the importance of these receptors.

Spontaneously hypertensive rats have an increased noradrenergic bladder innervation. They also have an increased voiding frequency[138] and urodynamic studies revealed a pronounced detrusor overactivity,[139] which was abolished by intrathecally, but not intra-arterially, administered α_1-adrenoceptor antagonists. This provides evidence for the involvement of a spinal α_1-adrenoceptor in micturition control. The role of spinal α_1-adrenoceptor mechanisms in the control of urinary bladder function in anaesthetised and in decerebrate, unanaesthetised female rats was investigated by Yoshiyama et al.[140] They found that the α_1-adrenoceptor-selective agonist phenylephrine increased the intercontraction interval and the pressure threshold for inducing micturition, but did not change bladder contraction amplitude. A large dose of phenylephrine completely blocked reflex voiding and induced dribbling incontinence. Doxazosin decreased intercontraction intervals, but did not change bladder contraction amplitude. Under isovolumetric conditions, doxazosin increased bladder contraction frequency and decreased bladder contraction amplitude.

The contribution of different subtypes of α_1-adrenoceptors (α_{1A}, α_{1B}, α_{1D}) in the lumbosacral spinal cord to the control of the urinary bladder was examined in urethane-anaesthetised rats.[141] It was suggested that different α_1-adrenoceptor subtypes were involved in the modulation of reflex bladder activity. Via α_{1A}- or α_{1B}-adrenceptors, an inhibitory control of the frequency of voiding reflexes is exerted, presumably by an alteration in the processing of bladder afferent input. α_{1A}-Adrenoceptors mediate facilitatory modulation of the descending efferent limb of the micturition reflex pathway. It was also concluded that spinal α_{1D}-adrenoceptors did not appear to have a significant role at either site.[141] This finding is of particular interest considering that in the human spinal cord α_{1D}-adrenoceptor mRNA predominates.[133] It should be noted that in the rat there is a high expression of both α_{1A}- and α_{1D}-adrenoceptor mRNA.[142]

Several studies have suggested that spinal and/or supraspinal α_2-adrenoceptors can modulate LUT function.[8] Smith et al.[143] performed *in situ* hybridisation to identify cell bodies containing α_2-adrenoceptor subtype-specific mRNA at the same four levels of the human spinal cord (cervical enlargement, thoracic, lumbar and sacral) as investigated for α_1-adrenoceptors.[143] α_2-Adrenoceptor mRNA was present in grey matter only and predominantly in the sacral region. Cervical spinal cord demonstrated a predominance of α_{2A}-adrenoceptor mRNA signal, while thoracic, lumbar and sacral spinal cord showed an increasing predominance of α_{2B}-adrenoceptor mRNA. This was different from findings in the rat, where α_{2A}-adrenoceptor and α_{2C}-adrenoceptor predominated.[144,145]

Ishizuka et al.[146] performed continuous cystometry in normal, conscious rats in the presence of α_2-adrenoceptor stimulation and blockade. The selective α_2-adrenoceptor agonist dexmedetomidine, given intrathecally, stimulated bladder activity and eventually caused total urinary incontinence. Intra-arterial dexmedetomidine decreased micturition pressure, bladder capacity, micturition volume, residual urine volume and basal pressure. The selective α_2-adrenoceptor antagonist atipamezole increased micturition pressure, bladder capacity and residual urine volume, and decreased micturition volume when given intrathecally, and similar effects were obtained with intra-arterial administration.

Kontani et al.[147] administered the α_2-adrenoceptor agonists clonidine and oxymetazoline (intrathecally or intracerebroventricularly) to conscious rats and demonstrated that both drugs induced detrusor overactivity, which could be prevented by the selective α_2-adrenoceptor antagonist idazoxan. The researchers suggested that this overactivity could be produced via α_{2A}-adrenoceptor stimulation both at spinal and supraspinal sites.

8.1 Therapeutic Effects and Opportunities

Animal data suggest that the α_1-adrenoceptors seem to mediate descending excitatory actions on the bladder and that they may also inhibit spinal

afferent transmission.[140] Clinically, α_1-adrenoceptor antagonists have been observed occasionally to abolish detrusor overactivity in patients with BPH.[148] α_1-Adrenoceptor antagonists have also been used to treat patients with neurogenic detrusor overactivity, with moderate success.[148] Whether the site of action is central or peripheral has not been established. Both efficacy and tolerability of α_1-adrenoceptor antagonists appear to have a centrally mediated component.[148] Asthenia and dizziness associated with α_1-adrenoceptor antagonist treatment may be related to a CNS action rather than a peripheral vascular effect. There is no evidence that these CNS effects are mediated via α_{1A}-adrenoceptors.[148] The α_{1D}-adrenoceptor subtype seems to be predominant in structures in the CNS involved with micturition but its functional involvement in the pathogenesis of OAB has not been established. Since the same receptor subtype within the CNS may mediate asthenia and dizziness, and the relief of bladder storage symptoms, α_{1D}-adrenoceptor subtype-selective agents may not provide improved tolerability but this has to be tested clinically.

Spinal α_2-adrenoceptors are also of interest. If the findings in conscious rats are predictive for effects in humans, blockade of spinal and/or supraspinal α_2-adrenoceptors may enhance bladder storage.

9. Conclusions

Preclinical studies in different animal models have shown that modulation of normal micturition and detrusor overactivity by drugs acting within the spinal cord or supraspinally is possible. Promising results, showing elimination of detrusor overactivity but leaving the normal voiding pattern intact, have been obtained in such models with drugs interfering with GABA mechanisms, 5-HT_{1A} receptors, μ-opioid receptors and α-adrenoceptors. However, considering the limited predictability of existing animal models for efficacy in humans, positive proof of concept studies in humans are mandatory. Such studies are scarce and further investigations are needed.

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