319P CLINICAL PHARMACOLOGY OF THE LOWER URINARY TRACT: NEEDS MET AND UNMET

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Problems with the main functions of the bladder, the storage and elimination of urine, are common. Such problems used to be the sole province of the surgeon, gynaecologist for women and urologist for men. However it is now realised that most lower urinary symptoms (LUTS) do not arise from surgically correctable pathology, and that the results of surgery do not encourage enthusiasm for it. LUTS are commonly due to difficulty in emptying the bladder from outflow obstruction in men or problems in storage of urine, such as stress incontinence in women, or an overactive detrusor muscle in men and women.

Outflow obstruction does not require immediate surgery in most men, and a period of watchful waiting is advised. During this time, drugs to relax the smooth muscle of the urethra (alpha adrenoceptor antagonists) or to shrink the prostate gland (5 alpha reductase inhibitors) can be given.

Stress incontinence is due to urethral sphincter weakness. Although the value of surgery has been recently questioned, the majority of moderate to severe cases will require surgical elevation of their bladder neck. However at least part of the closure mechanism is due to the mucosal, submucosal and smooth muscle layers. These are oestrogen sensitive, and so all women with stress incontinence should be treated conservatively first and with oestrogens if they are deficient in these hormones. Alpha adrenoceptor agonists have been disappointing so far, perhaps because of a lack of specificity.

The overactive or unstable detrusor muscle was never a surgically correctable condition. The main pharmacological thrust is the use of anti-muscarinic drugs, which are limited by their anticholinergic side effects. Better understanding of the muscarinic receptor subtypes leads the hope for more specific drugs acting solely on the bladder. As yet, only the new drug tolterodine seems to have less adverse effects, but not because of this mechanism; the reason why is not clear. Calcium channel blockers should be useful therapeutically, although they have been clinically disappointing, perhaps due to loss of effect on chronic dosing. Oestrogens are effective in reducing detrusor contractions in the laboratory, and may have a therapeutic role in the future. However, progestogens antagonise any possible benefit of oestrogens.

Future developments require better understanding of the underlying mechanisms causing LUTS, and more specific agonists and antagonists to the bladder and urethral structures.

320P INSIGHTS INTO THE NEUROTRANSMITTER CONTROL OF THE LOWER URINARY TRACT: POSSIBILITIES FOR DRUG THERAPY

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In order to effectively control bladder activity, and to treat urinary incontinence caused by bladder overactivity, identification of suitable targets for pharmacological intervention is necessary. Such targets may be found in the central nervous system (CNS) or peripherally. The causes of bladder overactivity are not known, but theoretically, increased afferent activity, decreased inhibitory control in the CNS and/or peripheral ganglia, and increased sensitivity of the detrusor to efferent stimulation, may be involved. Several CNS transmitters may modulate voiding, but few drugs with a defined CNS site of action have been developed for treatment of voiding disorders.

Potentially, drugs affecting GABA, opioid, 5-HT, noradrenaline, dopamine, or 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 the efferent neurotransmission or the detrusor musde itself. Antimuscarinic drugs, β-adrenoceptor agonists, α-adrenoceptor antagonists, drugs affecting membrane channels, prostaglandin synthetase inhibitors and several other agents have been used. However, none of them has been developed specifically for treatment of bladder disorders, and their efficacy, as judged from controlled clinical trials (when available), is often limited.

Recent information on the α-adrenoceptor, β-adrenoceptor (β_3), and muscarinic receptor subtypes of the human detrusor and outflow region can be the basis for the development of compounds with effect on bladder overactivity and with improved tolerance. New ways of decreasing acetylcholine release may represent a promising way of controlling bladder contraction. Potassium channel openers are theoretically attractive, but drugs available so far have had a preference for vascular over bladder smooth muscle, which has limited their clinical use. However, new drugs belonging to these group with an interesting profile of action have been developed.

Drugs decreasing afferent activity represent an attractive therapeutic approach transmitters of afferent nerves and their receptors are possible targets for pharmacological intervention. Tachykinins, such as substance P, neurokinins A and B and other neuropeptides, have been demonstrated in nerves of the lower urinary tract and shown to be able to influence bladder function. Agents affect these nerves by causing the release of tachykinins, such as capsaicin and resiniferatoxin, given intravesically can be effective in some cases of bladder overactivity, and agents antagonising tachykinin receptors may also be of therapeutic interest.

New drugs, specifically directed for control of bladder activity are under development and will hopefully lead to improved treatment of urinary incontinence.

321P OXIDATIVE STRESS AND ABNORMAL NEUROTRANSMISSION IN GENITAL SMOOTH MUSCLE

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Ageing is associated with increased plasma markers of oxidant stress and with impaired nitric oxide (NO)-mediated vasodilatation (Rodrigues-Martinez *et al.*, 1998). This impairment is likely to result from the ability of superoxide anion to destroy NO. The nitrergic nerves present in many major organ systems, including the urogenital tract, constitute another major physiological signalling system through which smooth muscle tone is regulated by the Larginine-NO pathway. It seems likely that this system too may be subject to impairment following enhanced destruction of NO by superoxide anion produced during oxidant stress. Indeed, the efficiency of nitrergic transmission has been reported to decline with age (Smits & Lefebvre, 1996) and this may contribute to age-related problems of neurotransmission, including the development of impotence in the male population (Feldman *et al.*, 1994). Elucidation of the effects of oxidant stress on nitrergic transmission is therefore warranted.

Tissues in which the effects of oxidant stress on nitrergic transmission have been investigated include the anococcygeus and its contiguous muscle, the retractor penis. Surprisingly, despite destroying the activity of authentic NO, a large number of superoxide anion generating agents, including pyrogallol, duroquinone, LY83583 and hypoxanthine/xanthine oxidase, produce little or no inhibition of nitrergic transmission in isolated preparations of rat and mouse anococcygeus or bovine retractor penis (BRP) muscle (Martin *et al.*, 1994; Lilley & Gibson, 1995; Paisley & Martin, 1996; Liu *et al.*, 1997). Thus, nitrergic transmission in these tissues appears particularly resistant to impairment by oxidant stress. These findings have been taken by some as evidence against the nitrergic transmitter being NO *per se*. We considered an alternative explanation for the resistance of nitrergic transmission to inhibition by oxidant stress, i.e. that the transmitter (NO) was protected from the destructive effects of superoxide anion. The most likely protective candidate was the Cu/Zn isoform of superoxide dismutase (SOD), the major extracellular and cytosolic scavenger of superoxide. We inhibited this enzyme in strips of BRP using the copper chelator, diethyldithiocarbamate (DETCA), and found that the normally resistant nitrergic transmission process was now susceptible to blockade by all superoxide anion generators tested. Moreover, the blockade was indeed due to inactivation of the transmitter by superoxide anion because it was reversed upon addition of authentic SOD or certain low molecular weight SOD mimetics (Martin *et al.*, 1994; Paisley & Martin, 1996; Mok *et al.*, 1998). A similar role for Cu/Zn SOD in protecting nitrergic transmission was subsequently established in the mouse and rat anococcygeus muscles (Lilley & Gibson, 1995; Liu et al., 1997). More recently, Lilley & Gibson (1996; 1997) found evidence in the mouse and rat anococcygeus, that antioxidant protection by ascorbate adds to that provided by Cu/Zn SOD. Indeed, these workers demonstrated that ascorbate is co-released with NO following activation of nitrergic nerves.

In conclusion, the presence of two vital antioxidant systems, namely Cu/Zn SOD and ascorbate, ensures that nitrergic transmission in urogenital smooth muscle is normally resistant to impairment by oxidant stress. It is possible, however, that pathological situations may arise in which these antioxidant mechanisms are overwhelmed. Consequently, strategies to elevate the activity of SOD or ascorbate may have a role in restoring impaired nitrergic transmission under such conditions of oxidant stress.

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322P PHOSPHODIESTERASE INHIBITORS: A NOVEL APPROACH TO COMBAT ERECTILE DYSFUNCTION

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Penile erection is a complex process involving the peripheral, central and endocrine systems. For penile tumescence to occur, the smooth muscle of the corpus cavernosum and related arterioles relax enabling increased blood flow into the trabecular spaces of the corpus cavernosum. During sexual stimulation, nitric oxide (NO) is synthesised and released from NANC nerve terminals in the corpus cavernosum and also from endothelial cells. Both neuronal NO synthase and endothelial NO synthase are believed to be important sources of NO. Nitric oxide activates soluble guanylate cyclase which converts 5'guanosine triphosphate (GTP) to 3',5' cyclic guanosine monophosphate (cGMP) which acts as an intracellular second messenger molecule to elicit corpus cavernosum smooth muscle relaxation and erection.

The pivotal role that NO plays in the erectile process can be demonstrated using animal and human tissue *in vitro* and animal models *in vivo*. Electrical field stimulation (EFS) or muscarinic receptor stimulation induces rapid relaxation responses in precontracted human corpus cavernosum. The relaxant effects of acetylcholine are dependent on the presence of an intact endothelium and are secondary to release of NO. The relaxation responses induced by EFS persist in the presence of atropine and guanethidine, are blocked by tetrodotoxin and are inhibited by inhibitors of NO synthase. Overall, these data suggest that activation of the NO/cGMP system in the corpus cavernosum plays a key if not pivotal role in initiating physiological responses responsible for penile erection.

The biological actions of cGMP in the corpus cavernosum, elevated as a consequence of NO activation of guanylate cyclase, are terminated by cyclic nucleotide phosphodiesterase enzymes (PDEs). Currently, there are at least seven families of PDE which can be characterised based on substrate specificity, inhibitor profile and sensitivity to calmodulin. In the human corpus cavernosum, the presence of PDEs 2, 3 and 5 have been demonstrated along with PDE4. The major cGMP metabolising PDE in the human corpus cavernosum is cGMP specific PDE5. Agents that inhibit the breakdown of cGMP by inhibiting PDE5 have the ability to augment the normal physiological pathway mediating erection by increasing the amount of cGMP available for relaxing the corpus cavernosum. Sildenafil, a potent and selective PDE5 inhibitor, is able to enhance NO-driven relaxation responses of the human corpus cavernosum induced by EFS by acting in this way.

Thus, sildenafil enhances the normal physiological neural pathway responsible for penile erection which underlies its clinical utility and efficacy as a treatment for patients with erectile dysfunction.