Meeting Report for the ASPET Ray Fuller Symposium: Lower Urinary Tract Disorders: Physiology, Pharmacology, and Therapeutic Approaches

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A 2-day ASPET/Ray Fuller symposium, entitled “Lower Urinary Tract Disorders: Physiology, Pharmacology and Therapeutic Approaches” sponsored by the American Society of Pharmacology and Experimental Therapeutics and organized by Michael G. Wyllie, Ph.D. (Urodoc Ltd., Herne Bay, Kent, UK) and James Sullivan, Ph.D. (Abbott Laboratories, Abbott Park, IL), was held at the Moscone Convention Center in San Francisco from July 6 to 7, 2002. The symposium focused on the current status of research in functional urogenital diseases, in particular benign prostatic hyperplasia (BPH), overactive bladder (OAB), and erectile dysfunction (ED). The highlights of the symposium were:

1. Results of the MTOPS (Medical Treatment of Prostatic Symptoms), a large, long-term outcome study in medical BPH treatment, were reported.
2. A novel K-ATP channel opener, A-278637, with efficacy in a pig model of OAB was reported.
3. YC-1 and two novel pharmacophores were reported to activate soluble guanylate cyclase, via binding to an allosteric site that is different from the NO-site, and facilitate penile erection in conscious rats.
4. Phase III clinical results for tadalafil and vardenafil, two new phosphodiesterase (PDE) 5 inhibitors, revealed these agents are efficacious in ED patients. Further clinical trials are needed to determine whether the overall benefit/risk profiles of these compounds are comparable or superior to sildenafil.

Dr. Wyllie opened the meeting with an overview of the urology market. He noted that agents for the treatment of BPH, prostate cancer, ED, and incontinence comprise 40, 35, 15, and 10% of the market, respectively. Although the urology market generates approximately $7 billion in annual sales, it represents a small segment of the pharmaceutical industry as indicated by the fact that atorvastatin (Lipitor; Pfizer, New York, NY) alone generates similar revenues. The launch of sildenafil (Viagra; Pfizer Central Research, Sandwich, Kent, UK) for ED has fostered awareness of this condition, increasing the number of patients seeking medical attention for this disorder. It is estimated that even with this increase only 8% of all patients suffering from ED are currently seeking help. Furthermore, a large number of patients are not diagnosed, and 50% of the patients seeking attention go untreated. This may be a characteristic of the lifestyle-drug segment or may be related to the concerns regarding the cardiovascular safety of sildenafil, dose splitting, or to the reassurance patients feel after a successful trial with the drug.

Dr. Wyllie covered the dynamics of the OAB segment, noting that 50 to 60% of the nursing home population suffers incontinence and that the use of nonpharmacological products for this condition has a significant economic impact in terms of direct and indirect costs. It was noted there are at present no pharmacological treatments for premature ejaculation or female sexual dysfunction, although there are active research programs in these areas. It was suggested these therapeutic classes could very well experience significant growth over the next few years.

Benign Prostatic Hyperplasia

Dr. Wyllie opened the discussion on BPH by reviewing data on its prevalence and treatment. BPH, which is a histological diagnosis, often leads to lower urinary tract symptoms (LUTS), including weak stream, urgency, frequency, and nocturia. The prevalence of LUTS increases with age in both

ABBREVIATIONS: BPH, benign prostatic hyperplasia; OAB, overactive bladder; ED, erectile dysfunction; MTOPS, Medical Treatment of Prostatic Symptoms; PDE, phosphodiesterase; LUTS, lower urinary tract symptoms; VR1, vanilloid receptors; P2x, purinergic receptors; KATP, ATP-sensitive potassium; SB-269970, (R)-3-[(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulfonyl]phenol; sGC, soluble guanylate cyclase.
males and females, suggesting that prostatic enlargement is not the sole cause for this condition. The medical treatment of BPH has consisted primarily of 5α-reductase inhibitors and α-adrenoceptor antagonists (α-blockers).

Finasteride, a 5α-reductase inhibitor, was the first drug specifically designed to treat BPH. As reviewed by Fouad K. Habib, Ph.D. (University of Edinburgh, UK), there are two isoforms, types I and II, of 5α-reductase. Whereas these proteins share about 50% sequence identity, they are encoded by distinct genes and differ in their pH dependence. Although 32 naturally occurring mutations of the type II isoform have been identified, mutations of type I 5α-reductase have not yet been reported. Certain mutations of type II 5α-reductase predominate in particular ethnic groups, with many of them displaying widely different pH optima. Although the primary effect of 5α-reductase inhibition is to decrease dihydrotestosterone formation, there is a poor correlation between the serum concentrations of this hormone and the amount of finasteride in the prostate. Interestingly, dihydrotestosterone exerts a positive feedback on the expression of 5α-reductase. Thus, inhibition of 5α-reductase inhibits prostatic growth directly and indirectly. Directly by reducing the prostatic dihydrotestosterone concentrations and indirectly by reducing the expression of growth factors and the number of growth factor receptors, such as the receptor for insulin-like growth factor I. Although finasteride is clinically well tolerated, its effects on prostate volume, urine flow rates, and subjective BPH symptoms are only moderate. Although it is selective for type II 5α-reductase, the more recently developed dutasteride inhibits both isoforms of the enzyme with similar affinity. The clinical consequences of selective type II versus dual inhibition are not yet clear. Dr. Habib proposed that the reduction in serum prostate-specific antigen, which is commonly observed during treatment, is not related to the primary mechanism of action of finasteride or dutasteride but rather to the direct effects of these drugs on androgen receptor-mediated regulation of gene transcription. Some plant extracts used to treat BPH, including those from saw palmetto (Serenoa repens) berries also inhibit 5α-reductase in vitro, although by a different mechanism than finasteride and dutasteride. It remains controversial whether the saw palmetto extract is active in vivo, however. α-Adrenergic receptor blockers are now the most widely used drugs for treating BPH. Martin C. Michel, M.D. (University of Essen, Germany) discussed recent studies questioning some of the original concepts regarding their action. Originally it was believed that α-blockers act primarily by blocking the α1A-adrenoceptor subtype, thereby relaxing the prostate smooth muscle and, perhaps, bladder neck and urethra. Although this theory explains the moderate effects of α-blockers on bladder-outlet obstruction, data now suggest it may only partly explain LUTS improvement with these agents. Thus, there is a poor correlation in BPH patients between obstructive (voiding) and irritative (storage) symptoms and urine flow rate at baseline, and highly α1A-selective antagonists have been reported to enhance urine flow rate but not to improve LUTS relative to placebo. This led to the conclusion that α1-adrenoceptors (possibly of the α1D-subtype) located in other tissues, such as bladder or spinal cord, may contribute to the reduction in LUTS. Based on the original use of α-blockers for hypertension, it was assumed that most of their adverse effects are secondary to their blood pressure lowering action. This is not supported, however, by clinical results with BP patients. In this case, a combination of factors, including a relatively low affinity for the α1D-subtype, smooth pharmacokinetic profiles, and selective partitioning into urogenital tissues, probably contribute to the improved clinical tolerability of modern α-blockers such as alfuzosin or tamsulosin.

One tenet of the traditional concepts regarding the use of α-blockers in BPH was that they relieve LUTS without affecting the natural history of the disorder. To study this directly, the MTOPS study was undertaken. This NIH-sponsored trial of 3047 patients compared the responses to placebo with the long-term (median treatment 5 years) effects of an α-blocker (doxazosin), a 5α-reductase inhibitor (finasteride), and the two drugs in combination. The primary endpoint of the study was progression of BPH, which was operationally defined as an increase in LUTS, the occurrence of acute urinary retention, the occurrence of urinary incontinence, recurrent urinary tract infections, or the emergence of renal insufficiency (which did not occur in any patient). The MTOPS study results were released recently at a meeting of the American Urological Association (Baltimore, MD). The data suggest that both α-blockers and 5α-reductase inhibitors slow the progression of BPH over time in a quantitatively similar, but qualitatively different, manner. Thus, the α-blocker seemed to be somewhat more effective in attenuating LUTS over time, whereas finasteride displayed greater efficiency with regard to preventing urinary retention, particularly in the later years of the study. Most interesting is that the drug combination attenuated BPH progression significantly more than either drug alone. Retrospective analysis of various other, more limited studies indicates that the beneficial effect of α-blockers on BPH progression is a class effect. The enhanced effectiveness of the combined α-blocker/5α-reductase was accompanied by an additive side-effect profile. Although it appears that patients will benefit most from the combination treatment, a more detailed inspection of the data is necessary before drawing this conclusion.

Bladder Overactivity

The discussion of drug targets for the treatment of OAB was introduced by William C. de Groat, Ph.D. (University of Pittsburgh, PA) and Alison F. Brading, Ph.D. (Oxford University, UK), who reviewed the central and peripheral mechanisms controlling micturition, respectively. They emphasized that OAB treatment should suppress involuntary micturition while at the same time facilitating voluntary voiding. Since the former is a fetal form of micturition and the latter an adult form, OAB can be considered a regressive form of bladder control.

Dr. de Groat reported that bladder filling is accompanied by activation ofafferent stretch-sensitive Aδ-fibers and chemosensitive C-fibers that feed into the spinal reflex control of urine storage. The Aδ-fibers can be further subdivided into low- and high- threshold mechanosensitive fibers and volume-sensitive fibers. Excitation of the chemosensitive C-fibers involves VR1, vanillloid receptors and P2X purinergic receptors. The activation of voiding is under the tonic inhibitory control of the pontine micturition center. Other important central nervous system regions that participate in the regulation of voiding include Onuf’s nucleus, the sacral
parasympathetic system, the sympathetic intermediolateral nucleus, and the periaqueductal gray. Although storage reflexes are primarily coordinated in the brainstem, voiding reflexes are largely controlled at the spinal level, voiding reflexes are primarily coordinated in the brainstem. Glutamate is the primary transmitter of the ascending pathways, whereas inhibitory pathways between the brainstem and the spinal cord use serotonin. Transmitter systems involved in the modulation of the neural control of voiding include GABA, enkephalins, acetylcholine, and dopamine. This neuroanatomical circuitry explains why spinal cord injury initially results in bladder areflexia that is followed by hyperreflexia accompanied by bladder-sphincter dyssynergia. Animal models of OAB displaying these characteristics have been developed. Studies indicate that the inhibitory serotonergic pathway between the brain stem and spinal parasympathetic center involves 5-HT\textsubscript{1A} receptors. Thus, activation of these sites directly with agonists, or indirectly with serotonin reuptake inhibitors such as duloxetine, may prove beneficial. Such drugs are now in late stages of clinical development for the treatment of stress incontinence.

As discussed by Dr. Brading, bladder function is controlled not only by the central nervous system but also by the spontaneous phasic activity of its smooth muscle. The frequency of the activity is greater in smaller mammals, with the magnitude rarely exceeding 10% of the maximal neurally evoked tone. The spontaneous phasic contractions are due to myogenic electrical activity and are enhanced in various types of OAB. Spontaneous activity also occurs in the urethra, where it is tonic rather than phasic. Interstitial cells, the number of which is increased in OAB, may be pacemakers for bladder smooth muscle. Voluntary voiding in the human is mediated almost exclusively by muscarinic receptors, although contractions in the unstable bladder may also involve other transmitters, such as ATP.

Effector transmitters in the urethra include acetylcholine, noradrenaline, and NO. The tissue response to nerve stimulation depends on the parameter being examined because different patterns of stimulation may activate different nerves. Afferent sensory nerve activity is modulated by receptors on the nerve terminals that have VR\textsubscript{1}, P\textsubscript{2x3}, and eicosanoid receptors, as well as by the urothelium, which releases ATP or NO, by suburothelial interstitial cells and by the motor activity of the smooth muscle. Smooth muscle activity involves muscarinic receptors, which may explain the beneficial clinical effects of muscarinic receptor antagonists in the treatment of OAB. Dr. Brading suggested that the complex arrangement of smooth muscle, interstitial cells, nerves, and different transmitters and receptors that are present provide many targets for developing new agents for the treatment of incontinence.

Against this physiological background, David R. Staskin, M.D. (Harvard University, Boston, MA) discussed the shifting definitions of OAB. Based on the 2002 recommendations of the International Continence Society, OAB is an empiric diagnosis used as the basis for the initial management of a patient presenting with urgency, with or without urge incontinence, that is usually accompanied by frequency and nocturia. Although in the past incontinence had been considered a leading symptom of OAB, only 37% of OAB patients experience it, with the majority of patients remaining “dry”. In contrast to the empirical diagnosis of OAB, “detrusor overactivity” should be diagnosed only when this condition has been proven urodynamically. Usage of the terms “motor urgency” and “sensory urgency” is no longer encouraged. Since the diagnosis of OAB is purely symptomatic, it is not surprising that the etiology is heterogeneous. Moreover, a placebo responder rate as high as 30% is characteristic for OAB, making it difficult to demonstrate superior efficacy with any new therapy.

Sharath S. Hegde, Ph.D. (Theravance, Inc., South San Francisco, CA) noted that because acetylcholine, acting on muscarinic receptors, is the primary efferent transmitter controlling bladder smooth muscle tone, it is not surprising that muscarinic receptor antagonists are a mainstay for the treatment of OAB. Based on receptor numbers, the M\textsubscript{2}-subtype is most prevalent in the urinary bladder of various species, including humans, although contraction is mediated almost exclusively by the M\textsubscript{2}-subtype. M\textsubscript{2} receptors, however, may be important as mediators of bladder smooth muscle contraction under some pathological conditions, including bladder denervation. It is unclear, however, whether recruitment of M\textsubscript{2} receptors also occurs in other forms of bladder disease, including OAB, and whether the effects of M\textsubscript{2} receptor stimulation are predominantly mediated by a reduction of cAMP formation.

The bladder also expresses M\textsubscript{1} and M\textsubscript{4} receptors that, in vitro, display presynaptic facilitatory and inhibitory effects, respectively. Their in vivo role, however, remains to be elucidated. A possible function of muscarinic receptors on the urothelium or in the central nervous system is regulation of bladder function. The extent to which blockade of these sites contributes to the therapeutic effects of muscarinic receptor antagonists remains unknown. Dry mouth is the most frequent and treatment-limiting side effect of muscarinic receptor antagonists. As with bladder contraction, the effects on saliva involve M\textsubscript{4} receptors, although M\textsubscript{1} and/or M\textsubscript{2} receptors may contribute as well. Interestingly, the subjective feeling of dry mouth is only loosely correlated to objective measures of salivary flow rate, raising the possibility that basal and stimulated salivation may be mediated by different mechanisms. It remains to be determined whether nonselective antagonists (such as tolterodine), more (such as darifenacin) or less (such as oxybutynin) M\textsubscript{3}-selective antagonists, or M\textsubscript{2}-selective antagonists, which are yet to be developed, offer the best efficacy/tolerability ratio. Recently, extended release formulations have been introduced for both oxybutynin and tolterodine. Both display an improved tolerability relative to their respective immediate release formulations. Thus, pharmacokinetic properties also appear to contribute to the tolerability of muscarinic receptor antagonists.

As noted above, ATP is released from the bladder urothelium, activating purinergic receptors on afferent C-fibers. Major insights into the role of purinergic receptors in the control of bladder function have come from studies with knock-out mice lacking P\textsubscript{2x3} receptors, P\textsubscript{2x1} receptors, or both. The data were discussed by Anthony P. D. W. Ford, Ph.D. (Roche Bioscience, Palo Alto, CA). Although conscious P\textsubscript{2x3} receptor knock-out mice do not exhibit alterations of filling cystometry at baseline or upon stimulation of vanilloid receptors by capsaicin, bladder hyporeflexia is apparent under anesthesia. The P\textsubscript{2} P\textsubscript{2x3} receptor knock-out mice have unusually large, full bladders. Although initial studies suggest an increased bladder capacity for these mice during cystometry, later experiments did not confirm this in con-
responses. Taken together, these data suggest that P2x receptors play only a minor role in basal bladder filling. After noxious stimuli such as capsaiacin and/or during anesthesia, however, they contribute to the control of bladder contraction. In agreement with these observations, Dr. Ford discussed findings presented by Lu et al. at a recent meeting of the American Urological Association, which demonstrated that a P2x3 receptor antagonist of undisclosed chemical structure reduces urinary frequency in spinal cord-injured rats with detrusor hyperreflexia. Based on these findings, Dr. Ford discussed a therapeutic potential for P2x inhibitors in disorders of urine storage and voiding.

Murali Gopalakrishnan, Ph.D. (Abbott Laboratories) discussed the possible role of potassium channel activators as relaxants of bladder smooth muscle. There are several types of potassium channels that differ in their structure. Among this group, the family of ATP-sensitive potassium (KATP) channels has received most attention. These channels are hetero-octamers containing four SUR and four Kir subunits. The SUR1, SUR2A, and SUR2B subunits are expressed in a tissue-specific manner with the combination of SUR2B and Kir 6.2 being the most frequently expressed octamer in smooth muscle. Moreover, a splice variant of SUR2B (exon 17 minus) is preferentially found in the bladder but not in other tissues. There is an excellent correlation among drug potencies at this splice variant in guinea pig, pig, and human bladder. Although such a splice variant offers the potential of selective drug targeting, none of the drugs tested thus far has been able to discriminate receptor subtypes. Previous attempts to develop bladder-selective potassium channel openers have failed as exemplified with ZD 6169. Dr. Gopalakrishnan reported on a new potassium channel opener, A-278637. This agent hyperpolarizes guinea pig bladder membranes with an EC50 of 102 nM and causes relaxation of rat bladder strips at 10 to 100 nM. Intravenous doses of 10 to 30 nmol/kg inhibit bladder contractions in anesthetized, obstructed pigs. These doses correspond to plasma concentrations of 8 nM. In contrast, the plasma concentration of A-278637 needed to lower by 15 mm Hg mean arterial pressure of conscious dogs is estimated at 389 nM. Thus, A-278637 exhibits a greater degree of bladder selectivity than other potassium channel openers, such as ZD 6169 or WAY 133537. In the absence of clinical data, it is unclear the degree to which preclinical selectivity predicts the clinical utility of potassium channel openers. A-278637 will not advance into clinical development because of suboptimal pharmacokinetic properties.

VR1 vanilloid receptors are present on afferent nerve fibers. Naoki Yoshimura, M.D., Ph.D. (University of Pittsburgh, Pittsburgh, PA) reported that VR1 receptors are non-selective cation channels with a high calcium permeability. These sites are activated by protons, heat in excess of 43°C, or by capsaiacin. The VR1 receptors are attractive as drug targets because C-fibers do not appear to contribute to normal conscious voiding and most C-fibers, but few Aδ-fibers, are capsaiacin-sensitive. VR1 agonists, such as capsaiacin or resiniferatoxin, initially activate afferent nerve fibers, leading to rapid and long-lasting desensitization. As reported by Birder at a recent meeting of the American Urological Association, VR1 knock-out mice show signs of unstable bladder and a reduced urothelial production of NO. Dr. Yoshimura reviewed clinical data with resiniferatoxin, a VR1 agonist. A prospective, single-blind, placebo-controlled, dose-escalation study following intravesical administration was conducted on 36 patients who were refractory to muscarinic receptor antagonists and suffered from neurogenic voiding disorders due to multiple sclerosis or spinal cord injury. Seven doses of resiniferatoxin were compared with placebo. Although the lowest doses (0.005–0.02 μM) were not significantly different from placebo, doses of 0.5 and 1.0 μM significantly decreased the number of incontinence episodes and enhanced cystometric bladder capacity. Adverse events in these patients were generally transient and only mild to moderate.

A poster presentation by P. Lluel (Sanofi-Synthelabo Recherche, Rueil-Malmaison, France) reported on SSR240600, a selective neurokinin NK1 receptor antagonist. In anesthetized female guinea-pigs, i.v. administration of 30 to 100 μg/kg of SSR240600 significantly reduced micturition frequency without affecting micturition pressure, urethral pressure, or urethral relaxation during micturition. These data suggest this compound may be useful as a treatment of human OAB. K. Read (University College London, UK) reported that intracerebroventricular administration of SB-269970 (10−30 μg/kg), a serotonin 5-HT3 receptor antagonist, increased the bladder threshold for micturition without affecting the urethral relaxation during micturition. Since similar doses administered i.v. were ineffective, it was concluded that SB-269970 acts mainly within the central nervous system.

**Erectile Dysfunction**

The prevalence and treatment of male, as well as female, sexual dysfunction were discussed by Michael A. Adams, Ph.D. (Queens University, Kingston, ON, Canada). He indicated that the prevalence of ED is not precisely known because surveys in different countries have yielded different results, from 30% in UK to 8% in Sweden. In his opinion, this is due to a lack of standardization in the demographic analysis. Furthermore, after the launch of Viagra, the prevalence has increased, probably reflecting a change in attitude or understanding of the condition. Since the definition of normal or abnormal sexual activity/performance is subjective, it could have changed with the increased awareness of ED. It is now believed there is a 50% prevalence of ED in 40 to 70 year old males. The population of men suffering ED is expected to grow to 320 million worldwide by 2025. Age, cardiovascular disease, hyperlipidemia, smoking, and diabetes are risk factors for ED, as well as the excessive use of alcohol, hormonal dysfunction, trauma, or neurological disorders. Some of these risk factors are modifiable or treatable, including lifestyle, cardiovascular disease, sexual technique, drug use, and hormonal dysfunction. Indeed, ED may be a signal for an underlying condition such as diabetes, hypertension, anxiety, depression, and cardiovascular disorders. In summary, ED is highly prevalent, it is age-related, it is under-diagnosed, and it remains under-treated in this growing population.

With regards to female sexual dysfunction, Dr. Adams
stressed its etiology is unknown. Possibilities include problems of arousal, desire, lack of satisfaction, painful intercourse, troubled intimacy, or a relation to the presence of ED in the partner. The prevalence of female sexual dysfunction is thought by some to be as high as the prevalence of ED in men. Thus, there is a significant unmet need in this area. Some of the limited treatments currently available include hormonal replacement in postmenopausal women and the female pump. There are no pharmacotherapies available for female sexual dysfunction. Initial clinical studies with sildenafil revealed no effect in women with arousal disorders.

The central neural control of male sexual reflexes was reviewed by Kevin McKenna, Ph.D. (Northwestern University, Chicago, IL). Sexual behaviors of male and female rats have been studied for decades using different endpoints, including lordosis of the female and the number of mounts, darting, intromissions, and ejaculation latency of males in the presence of a receptive female. Lesion studies provided the first information on the brain areas controlling these behaviors. Experiments have revealed the neurotransmitter systems important in these brain regions for controlling these behaviors. Dr. McKenna indicated that ejaculation is normally suppressed by neurons in the rostral medulla, a compact group of cells that is mainly serotoninergic. Because serotonin blocks the ejaculatory response several pharmaceutical companies are testing selective serotonin reuptake inhibitors for the treatment of premature ejaculation. Although the particular serotoninergic receptors involved in the neural control of the ejaculatory response are unknown, there is evidence suggesting that the 5-HT2α receptor subtype may play a critical role. Oxytocin is another central neurotransmitter released during sexual arousal and orgasm in both male and female rats, with an oxytocinergic projection from the paraventricular nucleus to the spinal cord. Moreover, the intrathecal injection of oxytocin induces penile erection in rats. The spinal control of sexual behaviors is under modulatory influence from higher brain centers, including the medial preoptic area, the paraventricular nucleus, the periaqueductal gray, and the nucleus paragigantocellularis.

The peripheral regulation of erectile function was reviewed by Karl-Erik Andersson, M.D., Ph.D. (Lund University, Lund, Sweden). The penis contains a rich sympathetic innervation of the corpus cavernosum and the vasculature. The corpus cavernosum smooth muscle is contracted by several endogenous substances, such as norepinephrine, prostanoioids, endothelins, and angiotensin II. Dr. Andersson indicated that adrenergic nerves in human corpus cavernosum contain tyrosine hydroxylase and neuropeptide Y, although the role of the latter is unclear. The α1-adrenoceptor is the main adrenergic receptor expressed in cavernosal smooth muscle cells, although α2-adrenoceptor antagonists (i.e., clonidine) can also contract these cells. Endothelins are locally produced and may contribute to the muscle tone, although their precise role is unknown. Although both ET-A and AT-B receptors are found in human corporal membranes, endothelin receptor antagonists are ineffective in treating mild-to-moderate ED. Inasmuch as the Rho-kinase pathway is activated in the human corpus cavernosum by norepinephrine and endothelin, the Rho-kinase inhibitor Y27632 relaxes cavernosal strips.

The critical role of NO was also reviewed by Dr. Andersson because NO is released by parasympathetic nerves upon sexual stimulation, causing relaxation of the corpus cavernosum. Both NO and YC-1 activate soluble guanylate cyclase (sGC) via independent allosteric sites, and YC-1 increases intracavernosal pressure in rats.

Membrane-bound guanylate cyclase also plays a role in the corpus cavernosal tone. Thus, guanylate cyclase B is found in human tissue and is stimulated by C-type natriuretic peptide, which relaxes the corpus cavernosum. Dr. Andersson estimates that four approaches are being pursued for the treatment of erectile dysfunction: α-adrenergic receptor antagonists, stimulation of sGC, stimulation of adenylyl cyclase, and PDE5 inhibitors. The modest efficacy of phentolamine and the negative results with the selective α1A receptor antagonist Ro70–0004/003, however, indicate that blockade of the inhibitory adrenergic tone in the corpus cavernosum is not enough to induce penile erection in humans. On the other hand, selective α1P-antagonists may be of interest since A-119637 can potentiate the effect of a low dose of apomorphine and facilitate penile erections in rats. The use of a combination of apomorphine and sildenafil may also offer advantages in terms of increased therapeutic efficacy and reduced side effects.

The preclinical and clinical data on PDE5 inhibitors were presented by Kenneth M. Ferguson, Ph.D. (ICOS Corp., Bothel, WA). Before the discovery of proerectile PDE5 inhibition, the treatment of ED was limited to the use of surgical procedures, pumps, or intracavernosal agents. Ferguson indicated that three PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) (Fig. 1) display a significant benefit in ED patients. Tadalafil potently (EC50 = 30 nM) increases relaxation induced by electrical stimulation of the corpus cavernosum and potentiates the effect of sodium nitroprusside. When erectile function is evaluated using the erectile domain score of the International Inventory of Erectile Function (IIEF) questionnaire, all three PDE5 inhibitors exhibit similar proerectile effects in ED subjects (placebo score: 15; drug-treated score: 22). Although the response is considered a return to normal in ED patients, there is room for improvement because these patients do not reach the maximum score of 30. One of the major differences between these three drugs is the longer half-life of tadalafil (~16 hs) compared with the others (~5 hs). For this reason, tadalafil was proposed as an agent that would allow a more natural sexual relationship since it can be taken long before any possible sexual activity. The prolonged half-life of tadalafil, however, may raise concerns about its safety because the long-term presence of the drug in the bloodstream increases the risk for drug-drug interactions in patients taking other medications (antihypertensives, hypoglycemic agents, hormones, etc.). Although tadalafil has received an approval letter by the FDA, further

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**Fig. 1.** PDE5 inhibitors for the treatment of ED.
The regulation of penile function by YC-1 (Fig. 2) and novel activators of sGC was presented by Jorge D. Brioni, Ph.D. (Abbott Laboratories). An important enzyme in corpus cavernosum smooth muscle cells, sGC regulates the intracellular levels of cGMP. It is physiologically activated by NO released after sexual stimulation, with the increase in cGMP levels inducing relaxation of the corpus cavernosum and penile erection. Dr. Brioni presented reverse transcription-polymerase chain reaction studies demonstrating that the α1β1 subunit is the major subunit expressed in human corpus cavernosum. Although YC-1 is an allosteric activator of sGC, it is not blocked by ODQ, a competitive antagonist of the NO-receptor site (Fig. 2). Thus, YC-1 does not act via the NO binding site to activate the enzyme (an NO-independent effect). YC-1 can further increase sGC activity in the presence of an NO-donor, such as sodium nitroprusside (an NO-dependent effect). YC-1 can relax rabbit cavernosal strips and increases cGMP levels in cultured rabbit cavernosal cells. Furthermore, systemic injection of YC-1 facilitates penile erection in conscious rats. Dr. Brioni disclosed two novel agents, A-344905 and A-350619, as pharmacophores that activate sGC. Kinetic studies in purified rat α1β1 subunits indicate they act via the YC-1 site to relax rabbit cavernosal strips and to facilitate penile erection in conscious rats after systemic administration. The validation of this as a potential target for the development of new agents for treating ED was discussed. These agents do not display cardiovascular effects in rats during continuous i.v. administration at plasma levels severalfold greater than those required to facilitate penile erection. Despite the fact that sGC is present in vascular smooth muscle cells, the lack of cardiovascular activity of A-344905 may be because PDE activity is intact in these cells. The need to conduct further cardiovascular studies in dogs and to determine the potential interaction with nitrates was highlighted. On the other hand, PDE5 inhibitors exhibit limited efficacy in the treatment of ED in diabetic patients, probably due to a diminished release of NO upon sexual stimulation. Agents that activate sGC and enhance the activity of endogenous NO in the corpus cavernosum may represent a novel approach to regulating penile function in humans, particularly those who fail to respond to PDE5 inhibitors.

The effects of dopamine receptor agonists in ED were reviewed by Michael A. Adams. He reported that activation of D₁ sites controls motor behaviors, the D₃ receptor participates in reward mechanisms, and the D₂ receptor controls penile erection. Dr. Adams stressed that psychological aspects of stimulatory or inhibitory mechanism can affect the induction of penile erection in humans. Therefore, understanding the different inhibitory mechanisms may shed light onto the pathophysiology of ED. Depression, anxiety, and fear are some of the inhibitory elements that affect penile erection and sexual performance in humans. Apomorphine (Uprima; Abbott Laboratories) was recently approved in Europe for the treatment of ED. Dr. Adams concluded that apomorphine acts predominantly at postsynaptic D₁ and the D₂ receptor subtypes, with activation of the D₂ receptor in the paraventricular nucleus enhancing the natural erectile response. Although it is known that injections of apomorphine in the paraventricular nucleus of the hypothalamus induce penile erection in rats, this may not be the only site of action of apomorphine, especially after systemic administration. For this reason, the effect of apomorphine in other limbic or cortical areas that regulate penile erection in hu-
mains should not be discounted at this time. Dr. Adams indicated that the sublingual formulation of apomorphine allows rapid absorption and onset of action; plasma levels are detectable in 10 min, and the onset of erection is ~20 min for 71% of the ED patients. There is an increase in the success rate after the continuous use of apomorphine, as 53% of the patients show a positive effect after the first attempt, whereas 74% benefit after six doses. Apomorphine also exhibits long-term efficacy at 6, 8, 12, and 18 months, with 93% efficacy maintained after this time. Thus, apomorphine represents a new mechanistic approach for the treatment of ED.

In summary, the ASPET/Ray Fuller symposium on lower urinary tract disorders brought together a group of basic and clinical investigators from academia and industry. It was apparent from this meeting there is considerable unmet medical needs in the field of functional urogenital disorders. The plethora of potential drug targets open possibilities for development of new therapeutics for the treatment of these conditions.

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