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"Urological Disease and Sexual Dysfunction in Animals"

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KEYWORDS

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ABSTRACT:

Numerous disorders are linked to lower urinary tract dysfunction or reduce the capacity for satisfying sexual activity, causing great distress to individuals with the illness, their partners, and/or caregivers. Some of the animal models that could be utilized to find safe and efficient medications to treat them are discussed in this article. While 5-alpha-reductase inhibitors and alpha adrenoceptor antagonists help patients with benign prostatic hyperplasia by improving their symptom relief, there are less effective and well-tolerated medications available to treat incontinence. In the US, muscarinic antagonists, sometimes known as anti-muscarinic, are the only approved medical treatment for overactive bladder (OAB) and stress urinary incontinence (SUI). High prevalence is a defining characteristic of SUI and OAB. an aging population and a significant desire for more efficacious treatment choices among patients and doctors. Sexual dysfunction in both men and women is characterized by high patient numbers and low presentation rates. When an efficient substitute for injections and devices is available, patients with erectile dysfunction are eager to seek treatment, as evidenced by the success of the phosphodiesterase type 5 inhibitor class (PDE5 inhibitor) and the 1998 launch of Viagra. Predicting clinical outcomes is the primary use of preclinical models in the search for novel medications. In fields of medicine where there are many medications with various underlying pharmacological mechanisms in clinical usage, this translation can be established rather readily. Still, aside from using PDE5 inhibitors, for instance There is little clinical data about the use of anti-muscarinic to treat OAB and male erectile dysfunction. Consequently, our current level of confidence in preclinical models is predicated on our comprehension of the physiological, pathophysiological, psychological, and pharmacological mechanisms underpinning human illnesses and how these mechanisms manifest in preclinical models. If several models representing related facets of the same condition produce corroborated results, confidence in the models employed as well as the pharmacological data produced is strengthened. But until the pharmaceutical drugs these models have assisted in identifying are tested on humans, they cannot be considered fully verified in retrospect.

Abbreviations: BP, blood pressure; BPH, benign prostatic hyperplasia; CI, cerebral infarcted; CNI, cavernous nerve injury model; CNS, central nervous system; EMG, electromyographic; EUS, external urethral sphincter; ICP, intracorneal pressure; IWT, positive ice-water test; IWT, negative ice-water test; LQ, lordosis quotient; LUT, lower urinary tract; MPOA, medial preoptic area; OAB, overactive bladder; PDE5, phosphodiesterase type 5; PVN, paraventricular nucleus; RBCs, rhythmic bladder contractions; NGF, nerve growth factor; SCI, spinal cord injury; SHR, spontaneously hypertensive rat; SSRIs, serotonin reuptake inhibitors; SUI, stress urinary incontinence; WKY, Wistar Kyoto; UG reflex, urogenital reflex.

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1. INTRODUCTION:

"Animal models of the function and malfunction of the lower urinary tract"

pee storage and periodic and timely emptying or expelling of the stored pee are the two main purposes of the lower urinary tract (LUT). This involves the autonomic and somatic nervous systems' intricate patterns of efferent (motor) and afferent (sensory) signaling. The involved nerves are a part of a reflex pathway that includes a conscious control component. This reflex pathway can either contract the detrusor smooth muscle of the bladder to initiate micturition, or it can relax the urethra, the area of outflow, and keep the bladder in an accommodating state, allowing urine to be stored at low intravesical pressure. When it comes to LUT function, pathological diseases can be broadly categorized into those that impact bladder function (such as overactive bladder) uterus(OAB), urge incontinence, urge without incontinence and frequency), as well as conditions that impact the function of the urethra, such as stress urinary incontinence (SUI).In order to properly research and create pharmacological treatments for urine incontinence, it is necessary to comprehend pathophysiological dysfunctional circumstances as well as the normal physiological regulation of continence. Using animal models that most closely mimic the human LUT in terms of anatomical and physiological function is crucial in this regard. Numerous animal species, including non-human primates, dogs, pigs, cats, rabbits, rats, guinea pigs, mice, and hamsters, have been used in the past to study LUT function (Harada et al., 1989; Kontani et al., 1992; Yoshimura et al., 1993; Danuser & Thor, 1996;Giuliani et al., 1996; Ghoniem et al., 1996; Watanabe et al., 19971999; Nickel & Venker-van Haagen, 1999; Palea & Pietra, 1999; Pandita et al., 2000; Bae et al., 2001; Calvert et al., 2001; Lecci et al., 2001), with most of these species having a number of anatomical, pharmacological, and neurophysiological characteristics in common with humans (DeLancey, 1990; Dwyer & Glenning, 1990; Birder & de Groat, 1993; Fletcher, 1996; Neuhaus et al., 1999; 2001; Dass et al., 2001; Ganzer et al., 2002; 2004; Silva & Karram, 2004). Nevertheless, it is important to take into account certain variations in the typical urinary tract structure and function across these species when extrapolating pharmacological or physiological results to possible human therapeutic interventions. Along with Numerous extensive reviews are available and advised to the reader with respect to current knowledge of the pharmacological therapy and comprehension of the LUT (de Groat & Yoshimura, 2001; Andersson et al., 2002; Moreland et al., 2004).

Models showing how the bladder works:

All species with the exception of humans and Old World monkeys have dual excitatory innervations to the bladder's smooth muscle, which are cholinergic (acetylcholine) and purinergic (ATP) (Brindley & Craggs, 1976; Craggs & Stephen- son, 1985; Craggs et al., 1986; Fujii, 1988; Brading & Mostwin, 1989; Sneddon & Mclees, 1992; Hashitani et al., 2000; Vial & Evans, 2000; de Groat & Yoshimura, 2001; Pessina et al., 2001). This is believed to be because certain species have evolved to mark or scent their territory with urinal. However, research has demonstrated that P2X1 (functioning ATP receptors) are expressed by normal human bladder smooth muscle cells (Inoue & Brading, 1991; Bayliss et al., 1999; Elneil et al., 2001). Remarkably, functional purinergic innervation may be demonstrated in bladder smooth muscle from patients displaying pathological conditions like obstruction or interstitial cystitis (Palea et al., 1993; Bayliss et al., 1999; Andersson, 2002), implying that the mere fact that such innervation is present in animal models does not negate their potential significance. Rats and humans differ significantly anatomically in that the postganglionic parasympathetic cell bodies that innervate the rat bladder are entirely located in the pelvic ganglia, whereas in other species, a large number of these cell bodies are contained inside the bladder wall; while it is known that, in contrast to other species, the bladder from obstructed rats does not experience partial denervation, the possible significance of this in the interpretation of in vivo investigations in the rat has received little attention (Gabella & Uvelius, 1990). urinary cytometry The most widely used method for studying bladder function, regardless of

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species or model, is cytometry (Doi et al., 1999; Pandita et al., 2000; Testa et al., 2001; Gu et al., 2002). This involves slowly filling the bladder while monitoring intravesical pressure through a bladder dome or urethral cannula until the point of fullness in order to elicit a micturition or voiding response (Figure 1); it can be carried out on either conscious or anesthetized animals with the use of telemetry, but in conscious animals, it's also advisable to measure intra-abdominal pressure to account for transmitted pressure rises from the abdomen hollow. Thus, it is possible to evaluate how medications, nerve stimulation or ligation, or intravesical treatments affect bladder function. Likewise, cytometry can be employed to evaluate the variations in bladder function between control and pathology-injected mice (Pandita et al., 2000) or between normal and knockout animals (Cockayne et al., 2000; Birder et al., 2002). Most studies have identified bladder capacity, threshold pressure, micturition pressure, and residual volume as measurable end points. Additionally, the pressure–volume relationship during bladder filling can be used to infer a measure of bladder wall compliance (Figure 1). Numerous investigations have indicated that animals may experience modifications in cytometric parameters that are similar to those observed in humans. following the administration of medications such as the TRPV1 activators capsaicin and resiniferatoxin (Ishizuka et al., 1995) and the GABAB receptor agonist baclofen (Giuliani et al., 1992; Igawa et al., 1993; Watanabe et al., 1997). Comparably, it has been demonstrated that anti-muscarinics used in clinical settings lower micturition pressure in animal models (Modiri et al., 2002). These findings imply that the fundamental regulation of micturition, which is observed in animals during conscious or anaesthetized cystometry, is representative of human micturition regulation. This is especially relevant in light of the fact that cystometry can be used to examine bladder function clinically (Flisser & Blaivas, 2002). Cytometry that is isovolumetric The isovolumetric model, a variant on standard bladder cystometry, studies the urine bladder's behavior following acute and thorough closure or obstruction of the urethra and bladder neck, which eliminates the bladder's capacity to empty and establishes an isovolumetric system (Figure 2a). The isovolumetric state is most frequently used in rats. When the bladder is filled, its volume rises until a micturition event occurs. At that point, filling is halted, and the bladder continues to produce rhythmic isovolumetric contractions with comparable amplitude, frequency, and duration. Subsequently, it is possible to examine how medications or other stimuli affect the frequency and amplitude of rhythmic bladder contractions (RBCs) (Figure 2b; Birder & de Groat, 1993; Lecci et al., 1993). One clear drawback of this approach is the possible harm that could be inflicted upon the innervation of the proximal urethra and bladder neck, especially when ligation is used. On the other hand, techniques for blocking the neck of the bladder while maintaining urethral perfusion enable the examination of the effects of the urethral reflex on bladder activity. Numerous studies have demonstrated effects with drugs known to alter measured parameters during standard cystometry, but the interpretation of drug effects must take into account what is known about normal bladder function due to the highly non-physiological nature of isovolumetric investigation. When given intravesical, capsaicin and resignification have both been demonstrated to produce an early rise in RBC frequency followed by a protracted suppression (Cheng et al., 1999; Komiyama et al., 1999), indicating the significance of afferent When RBCs are present, TRPV1-expressing nerve fibers are involved. It's interesting to note that studies examining c-fos expression in L6 spinal cord neurons during normal cystometry revealed elevated expression of c-fos, primarily in the sacral paralympic thetic nucleus region, with some staining visible in the dorsal commissure. Comparatively, isovolumetric cytometry and nociceptive stimulation/irritation with intravesical acetic acid both significantly increased the amount of c-fos-positive cells in the dorsal commissure (Birder & de Groat, 1993). 5-HT1A is Both the ORL-1 agonist nociception and the antagonist WAY100635 have been demonstrated to raise bladder capacity in standard cytometry (Giuliani et al., 1998; Testa et al., 2001) and to dose-dependently suppress RBCs (Lecci et al., 2000; Kakizaki et al., 2001).

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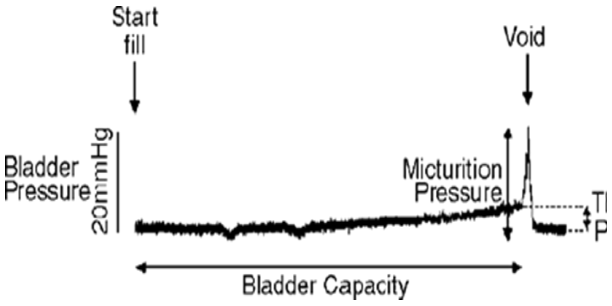

Figure 1 An example trace of normal bladder cytometry in a urethane-anaesthetised guinea-pig. As saline is infused into the empty bladder (Start Fill) at a constant rate, bladder pressure initially remains low; however, as bladder volume increases, a slow rise in intravesical pressure is evident. Bladder filling continues until a threshold volume (which is equivalent to the bladder capacity) and threshold pressure (equivalent to the difference in pressure between that at the initiation of filling (baseline pressure) and that measured immediately prior to the initiation of the voiding response) are reached to initiate micturition. At this time, urethral pressure decreases and bladder pressure increases (micturition pressure) in order to allow expulsion of bladder contents.

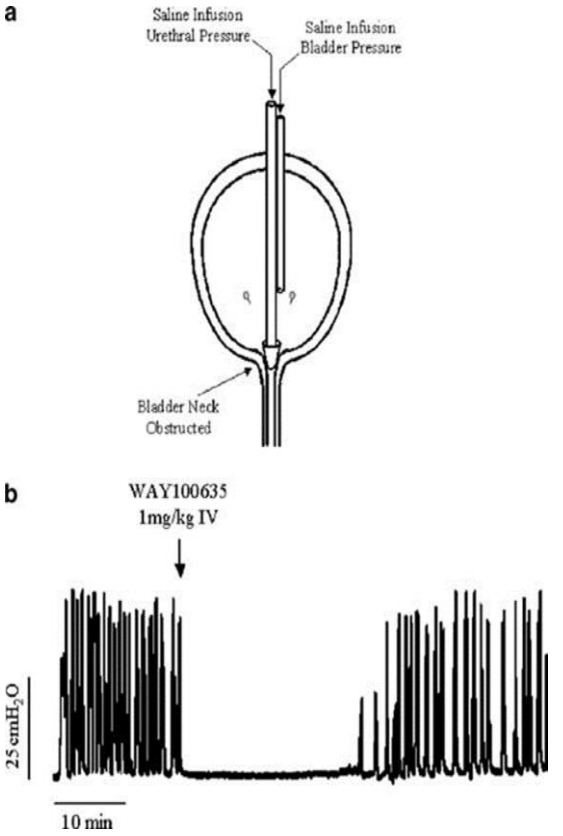

Figure 2 Isovolumetric bladder cytometry. (a) In order to achieve isovolumetric conditions during cytometry, the bladder neck is obstructed either via the external urethral meatus, in which case only bladder pressure can be measured, or via the bladder dome as shown, in which case both bladder and urethral pressure can be measured. (b) Upon filling, bladder volume increases until a micturition reflex is evoked, and when bladder filling is stopped, the bladder continues to exhibit reflex, RBCs. The 5-HT1A antagonist WAY100635 inhibits such reflex contractions.

Inflammatory cystometry Using a substance other than saline to infuse into the bladder in order to cause a painful sensory or irritating response—especially through C-fibers—is another variation on bladder cystometry. While other agents have comparable effects, acetic acid (up to 1% v v—1) is most frequently utilized as the chemical irritant. When acetic acid is infused into the bladder, the micturition pressure either stays normal or rises, but the bladder's activity, capacity, and voided volume decrease and compliance increases. It is believed

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that acetic acid produces these effects by activating nociceptive afferent fibers in the bladder wall, which may replicate the heightened sensory activity seen in OAB and urge the enhanced sensory activity that is assumed to be present in urge and OAB (Fowler, 2002). The results indicating higher c-Fos expression occurs in rat spinal cord and in regions of the periaqueductal gray with acetic acid in comparison to saline infusion provide evidence for an increased sensory component during irritative cytometry (Birder & de Groat, 1993; Mitsui et al., 2003). The increase in c-Fos expression that results from acetic acid infusion is mediated, at least in part, by TRPV1-expressing afferent neurons, according to similar studies comparing control rats to those that had previously been exposed to resignification in order to desensitize bladder afferent fibers (Avelino et al., 1999). Other researchers have demonstrated that acetic acid had no effect on bladder capacity or activity. acetic acid cytometry's facilitative effects on bladder function were also observed in rats treated with resignification (Zhang et al., 2003) and in rats in which the hypogastric nerves had been transected (Mitsui et al., 2001), further indicating the importance of sensory input. While irritative cytometry is a valuable tool for identifying compounds or mechanisms that are important to bladder function and may be used to treat bladder dysfunction, it should be kept in mind that acetic acid infusion, especially at commonly used concentrations, will cause significant damage to the bladder urothelium and induce a significant localized inflammatory response within the bladder wall. As such, care should be taken when interpreting the effects of compounds known to affect inflammatory mechanisms. In an effort to lessen the possibility influence of inflammation, a less irritating substance like citric acid can be employed as well. Citric acid (1–10 mg ml—1, pH 4–4.5) bladder cystometry exhibits effects that are comparable to those of acetic acid in that it decreases bladder capacity, increases bladder activity, and decreases compliance (Figure 3a); nevertheless, histological analysis of bladders from control and acetic acid-treated whereas mice given citric acid demonstrated less inflammation and urothelial damage (Figure 3b). the ice-water test Clinical studies have demonstrated that patients with neurogenic bladder overactivity, such as those with spinal cord damage, Parkinson's disease, multiple sclerosis, or different cerebrovascular lesions, have an enhanced sensitivity and response (Balmaseda et al., 1988; Geirsson et al., 1993; 1995; Ishigooka et al., 1997; Ronzoni et al., 1997; Ismael et al., 2000). swift injection of freezing-cold saline into the bladder. This is characterized by persistent involuntary

The positive ice-water test (IWT) is defined by contractions of the bladder and voiding at a threshold volume that is less than the typical cytometric capacity when warm saline is injected at a similar pace. A spinal reflex loop involving C-fiber afferents is hypothesized to mediate this bladder-to-bladder excitatory response; those with adequate bladder function do not show an IWT (Geirsson et al., 1993; Ishigooka et al., 1997). The majority of elderly patients with uninhibited OAB who did not have a neurological diagnosis but who may have had a specific, limited, but undiagnosed neuropathy were found to have an IWT (Geirsson et al., 1993); patients with bladder overactivity due to obstruction have also been shown to have a high incidence of IWTs (Chai). while other studies have not corroborated such findings. & al., 1998; Gotoh et al., 1999; Hirayama et al., 2003) and in children under the age of four (Geirsson et al., 1994). Spinal cord injured individuals who had previously experienced bladder hyper-areflexia and an ice-water test (IWT) improved in bladder function and had a negative IWT following intravenous therapy with capsaicin, confirming the sensory basis of this response (Geirsson et al., 1995). Anaesthetized cats and guinea pigs have shown a similar cold-induced bladder reflex response (Fall et al., 1990; Mazieres et al., 1998; Jiang et al., 2002; Gardiner & Westbrook, 2003), but not anesthetized rats (Cheng et al., 1997). The guinea pig's reflex has been shown to potentially involve afferent C-fibers. been determined by pretreating these species with resignification, which inhibits an IWT (Gardiner & Westbrook, 2003). Animal versions of the ice-water test have been reported on relatively rarely, although they provide an additional measure of sensory regulation and function throughout the micturition

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cycle and can be used for direct comparison with clinical investigations.

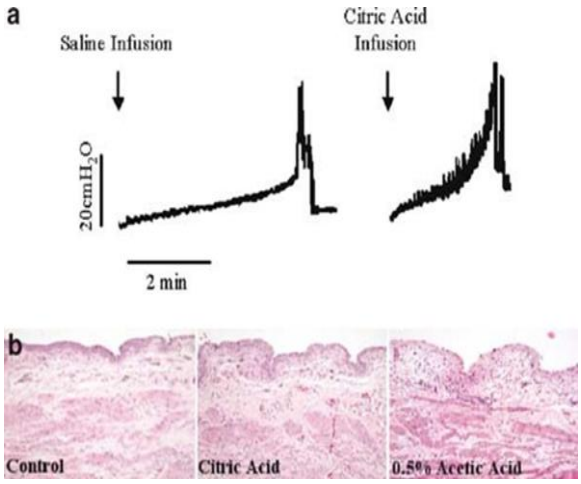

Figure 3 Citric acid bladder cystometry in a urethrane-anaesthe- tised rat. (a) Infusion of saline into the bladder results in a normal cystometrogram and voiding reflex. Subsequent infusion with citric acid (1 mg ml—1, pH 4.5) leads to shorter filling interval and hence bladder capacity, development of bladder hyperactivity and reduced compliance. (b) Sections of bladder wall (haematoxylin and eosin) from animals treated with saline, citric acid and acetic acid. Note damage to the urothelium (arrow) and suburothelial neutrophilia (*) in the acetic acid-exposed bladder.

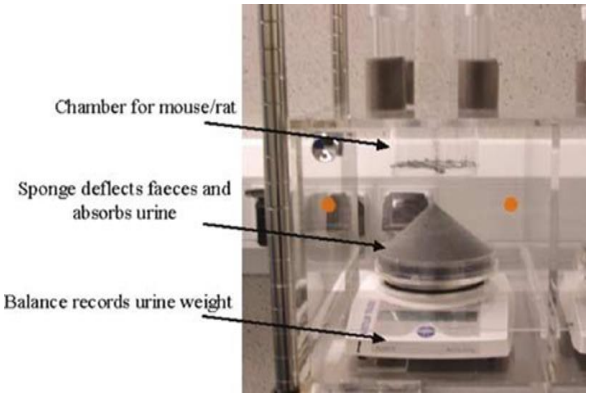

Figure 4 Meta bowl equipment for conscious evaluation of drug effect on normal diuresis filled bladder function and void volume. Different-sized chambers allow for both rat and mouse conscious voided volume experiments and combined with telemetry allow for measurement of bladder pressure and other parameters.

can be measured (thanks to Lewis, S., Pfizer is accomplished by looking into the typical amounts and frequency of voiding that occur during a typical filling in aware animals. This can be done by putting the animals in separate meta bowls that have been volume-loaded with saline beforehand or that have unrestricted access to water for three hours. Each animal's absence of urine can then be seen on a conical sponge that was positioned in a container under every metabowl (Figure 4). A balance is positioned directly beneath the collection container to measure the total volume of urine that was voided within the 3-hour period as well as the volume of urine per void. To guarantee that the balance records only the volume of urine, faecal pellets are either deflected by the sponge or caught on a wire frame above the sponge. The average volume of urine per void, the total volume voided and the frequency of voiding events can be compared between vehicle- and drug-treated animals, wild-type and knockout mice or animals in which a pathological state has been induced. Changes in these variables, in the absence of changes in the total urine output, are suggestive of changes in LUT performance. This method can also be used in conjunction with telemetry probes to monitor motor activity, body temperature, and bladder pressure. It can also be used to look into bladder activity that is captured during voiding episodes. Prior conscious investigations examining bladder function in a variety of species, including humans, monkeys, and pigs, have found success with telemetry (Thuroff et al., 1981; Miyagawa et al., 1986; Ghoniem et al., 1997; Mills et al., 2000; Fey et al., 2003). With these techniques, several parameters can be continuously monitored without the need for anesthesia, tethering, or restriction in a stress-free and physiologically realistic setting. blockage of the bladder outflow Men's OAB is frequently linked to urethral blockage brought on by benign prostatic BPH, or hyperplasia. Partial urethral obstruction with a ligature that either occludes the urethra immediately or gradually obstructs it as the animal grows has produced similar results in a number of animal species (Sibley, 1985;

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1987; Kato et al., 1988; Pampinella et al., 1997; Bao Jun et al., 2000; Pandita et al., 2000; Calvert et al., 2001; Wolffenbuttel et al., 2001; Das et al., 2002). These kinds of models show many of the structural and physiological bladder wall changes as those seen in human obstruction including increased spontaneous myogenic activity, altered responsive- ness to stimuli, patchy denervation of the smooth muscle (although not in the rat; Gabella & Uvelius, 1990), muscle hypertrophy, enlarged sensory neurones and parasympathetic ganglia and increased effectiveness of a spinal micturition pathway (Dupont et al., 1995; Brading, 1997; Turner & Brading, 1997). During conscious or anaesthetised cystometry, obstructed animals have often been shown to exhibit increased bladder capacity, residual volume, threshold pressure and micturition pressure in addition to the occurrence of non- voiding contractions (Sibley, 1985; Mostwin et al., 1991; Igawa et al., 1994; O'Connor et al., 1997). Mechanisms known to directly relax bladder smooth muscle, such as b3 adrenoceptor agonists or potassium channel openers, have been shown to be effective in reducing these non-voiding contractions (Woods et al., 2001; Fabiyi et al., 2003). A major factor thought to underlie neuronal, particularly afferent, plasticity in animal models of obstruction and in the human condition is the increased levels of nerve growth factor (NGF) released within the bladder wall (Steers et al., 1991). Further support for the importance of NGF in animal models is the finding that rats immunised with mouse NGF in order to develop autoanti- bodies did not develop neural plasticity and urinary frequency in response to obstruction (Steers et al., 1996). Afferent plasticity has also been suggested by the increased effective- ness of tachykinin receptor antagonists in affecting micturi- tion parameters in obstructed as compared to control rats (Ishizuka et al., 1994; Bao Jun et al., 2000). Animal models of obstruction offer a system in which unstable contractions are present and occur in conjunction with chronic changes in both afferent and efferent innervation. However, it should be noted that in this model, such changes are the result of a specific insult that is not thought to occur in the great majority of OAB sufferers. Spontaneously hypertensive rat The spontaneously hyper- tensive rat (SHR) is a genetic model of hypertension, which is also known to exhibit abnormal bladder function; in parti- cular, SHRs have been shown to have reduced bladder capacity and voided volume, increased urinary frequency and increased occurrence of non-voiding contractions in compa- rison to their genetic control strain the Wistar Kyoto (WKY) rat (Persson et al., 1998; Tang et al., 2002). A number of differences in the in vitro activity of bladder smooth muscle have also been shown between SHR and WKY strains, indicative of fundamental changes in the innervation and physiological response to stimulation of the bladder in SHRs (Tong et al., 1996; Persson et al., 1998; Rajasekaran et al., 2005; Schneider et al., 2005). Although the exact cause of this altered bladder behaviour is not fully understood, a major factor may be the increased NGF levels that have been shown to be produced by bladder smooth muscle from SHRs (Clemow et al., 1998; 1999; 2000; Sherer et al., 2000), a factor that is also thought to at least partly underlie the development of hyperactive voiding in obstructed animals. Interestingly, it has also been shown that bladders from SHRs show increased levels of calcitonin gene-related peptide immunoreactive fibres (presumably afferent) and that neuronal cross-sectional area profiles for bladder afferents in the L6–S1 dorsal root ganglia are significantly larger in SHRs than in WKY animals (Clemow et al., 1997; Jahed & Kawaja, 2001). A similar increase in cross-sectional area was also found for bladder neurones within the major pelvic ganglia in SHRs (Clemow et al., 1997). Both these findings are similar to changes associated with obstruction (see above). Further evidence for a similar phenotype in this species in comparison to the pathology caused by urethral obstruction comes from the finding that a1-adrenoceptors antagonists produce a much more pronounced effect on micturition parameters in both SHRs and obstructed rats in comparison to WKY or control animals (Persson et al., 1998; Gu et al., 2002; Tang et al., 2002). As such, it has been suggested that the SHR represents a model in which changes in neuronal morphology and function similar to those that occur with obstruction are present in the absence of inducing an inflammatory insult in the form of

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urethral ligation. In particular, there appear to be specific changes in the sensory innervation of the bladder in this species. The potential importance of the afferent innervation in this model can be highlighted by the finding that intrathecal application of antisense oligonucleotide against the tetrodo- toxin-resistant sodium channel (Nav1.8) reduces bladder hyperactivity (Lee et al., 2002). Spinal cord injury The most commonly utilised and highly informative model of a central lesion with respect to LUT function is that of spinal cord injury (SCI). SCI is known to result in bladder dysfunction, including detrusor hyper- reflexia, in humans (Erickson, 1980; Colachis, 1992; Maders- bacher, 1999). Not surprisingly, similar effects can be seen in animal models (primarily cats and rats) of spinal cord lesion (for review, see Yoshimura, 1999; de Groat & Yoshimura, 2005), and such models have contributed to a greater under- standing of the spinal control of bladder function. In such models, SCI rostral to the lumbosacral level disrupts voluntary and supraspinal control of voiding and induces a considerable reorganization of the micturition reflex pathway. Following SCI in animals, the urinary bladder is initially areflexic, but can then become hyper-reflexic due to development of a spinal micturition reflex pathway, which occurs through plasticity of neuronal connections within the spinal cord; in addition, detrusor-sphincter dyssynergia also commonly develops (de Groat, 1995; de Groat & Yoshimura, 2005). A major factor involved in the initiation of bladder hyper-reflexia is thought to be additional changes in the afferent C-fibre control of the bladder following recovery from SCI (de Groat et al., 1990; de Groat, 1995). In particular, it is thought that the normally silent C-fibres, which do not typically respond to bladder distension during filling, become predominant in the afferent limb of the reflex (de Groat et al., 1990) due to an increase in excitability, which leads to mechanosensitive. It has been suggested from studies in rats that one of the underlying causes of this increased excitability is a shift in the expression of Naþ channels from a high-threshold TTX-resistant type to a low threshold TTX-sensitive type (Yoshimura & de Groat, 1997). A further finding in chronic spinally injured rats is that these C-fibers may, with time, change their phenotype to one resembling Ad-fibre bladder neurons, which do not respond to capsaicin (Yoshimura et al., 1998). This is not thought to be the case in chronic paraplegic cats (de Groat et al., 1990; Cheng et al., 1999) or in humans (Marianne de Se` ze et al., 1998), as capsaicin is effective in affecting micturition parameters. As such, spinal cord-injured animals, particularly According to Walter et al. (2005), cats provide a dependable model for studying spinal reflex pathways, the regulation of micturition following spinal cord injury, and the possibility of manipulating this process using electrical stimulation devices to treat bladder dysfunction in individuals with spinal cord injuries. Furthermore, in order to determine the impacts on bladder hyper-reflexia, these models are helpful in examining the impact of mechanisms that are known to act on C-fiber afferents or directly on the smooth muscle of the bladder or its innervation. However, the unique nature of the illness implicated must be taken into consideration when interpreting results to other forms of overactivity in the bladder in men. Models of an injury or central lesion In addition to SCI, certain illnesses of the central nervous system (CNS) are known to be linked to Urinary incontinence in humans is most frequently linked to central lesion conditions, including Parkinson's disease, multiple sclerosis, and stroke (Joseph & De, 2001; Sakakibara et al., 2001; Andersson & Pehrson, 2003). It follows that the aberrant bladder phenotype observed in some animal models of artificially produced central lesions is not surprising. Animals who have Parkinsonian symptoms and lesions caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in particular show decreased bladder capacity and overactivity during conscious or anesthetized cystometry (Albanese et al., 1988; Yoshimura et al., 1993; 1998; Dalmose et al., 2004). When 6-hydroxydopamine is injected into the substantia nigra pars compacta of rats to produce Parkinsonian-like symptoms, similar effects on urine bladder function have been seen (Kamo et al., 2003). Similar results are observed. In stroke models in animals, cerebral infarction resulting from closure of the middle cerebral artery in rats causes notable ischemia in the putamen and cortex, brain regions

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that are known to play crucial roles in the regulation of micturition. It has been demonstrated that this causes both acute and chronic increases in frequency, overactivity, and decreased bladder capacity (Yokoyama et al., 1997; 1998; 2000). In contrast to the MPTP-induced bladder hyperactivity model, the cerebral infarcted (CI) rat has been used in numerous studies to examine the effects of medications. Research has demonstrated that the D2 receptor antagonist sulpiride and the NMDA receptor antagonist dizocilpine or MK-801, either separately or in combination, enhanced bladder capacity in CI animals but not in control animals, indicating a function for glutamatergic and The development of bladder dysfunction is attributed to dopaminergic stimulation. Comparably, there is proof that cyclooxygenase-2 and nitric oxide synthase are involved in bladder hyperactivity following cerebral artery blockage in rats. It has been demonstrated that medications such as potassium channel openers, calcium channel antagonists, and muscarinic antagonists, which are known to modify bladder function in other animal models, also impact bladder capacity and overactivity in CI rats (Nakamura et al., 1999; Birder et al., 2002; Yokoyama et al., 2005). Models of this kind typically require caution when interpreting drug action on the micturition response because of the possibility that the drug mechanism directly contributes to lesion-induced effects. Female urethral function models Like bladder function models, we usually have to take before analyzing, take into consideration any structural or physiological variations between the various species and man. outcomes in terms of potential therapeutic benefit. The majority of studies on urethral and pelvic floor function in relation to therapeutic possibilities or animal models of SUI are conducted in female animals since SUI is more common in females. Monkeys (Ganzer et al., 2004), pigs (Dass et al., 2001), dogs (Augsburger & Cruzorive, 1995; Nickel & Venker-van Haagen, 1999; Ganzer et al., 2002), cats (Fletcher, 1974; 1996), rabbits (Khanna et al., 1981; Cruz et al., 2002), guinea-pigs (Neuhaus et al., 1999), rat (Poortmans & Wyndaele, 1998; Praud et al., 2003) are among the species that have been structurally compared to women. Most people agree that although intraurethral pressure surpasses the bladder's internal pressure, continence will be preserved. Every species uses the striated and smooth muscles of the urethra to produce a urethral sphincter, which works in tandem with the pelvic floor to help maintain continence. Pressure is produced in the urethra itself by the passive mechanism of the vascular urothelium, which can form an effective seal, as well as the active mechanism of both smooth and striated muscle contraction. There can be differences in the actual distribution of striated and smooth muscle between species. For example, it is believed that striated muscle occupies more than two-thirds of the exterior surface of the urethra in women (DeLancey, 1986; Yucel & Baskin, 2004). This is believed to be fairly comparable in the guinea pig, although in Approximately 50% of the urethral length in dogs and 20% in pigs are made up of striated muscle. Before extrapolating to humans, this has clear implications for the possible significance of different muscles in maintaining continence in different species. It should be taken into account while examining changes in urethral function with pharmacological mechanisms. Electromyographic activity of the external urethral sphincter It is believed that the striated external urethral sphincter (EUS) plays a significant role in the human and other species' continence mechanism, especially during periods of elevated abdominal stress or pressure (Brading, 1999). The assessment of electromyographic (EMG) activity during bladder filling or other urinary tract manipulation is a commonly used technique for indirectly assessing EUS function. These measurements have brought to light Certain animals and humans have different urethral functions; several species are believed to use their urethral striated sphincter both during the micturition process and during the storage phase. According to Conte et al. (1991) and Streng et al. (2004), the EUS in rats is assumed to be active during micturition and to have a significantly smaller part in preserving continence during anesthetic cystometry. The EUS actually becomes more active during micturition than it does before the micturition response begins, according to an EMG recording of female rat EUS activity (Figure

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5a), with a bursting of activity during voiding. Recordings of bladder pressure taken during the micturition phase, in which oscillations in peak pressure coincide with EUS EMG activity, also show this activity. In the literature, these oscillations are commonly referred to as intraluminal pressure high-frequency oscillations. They are believed to be caused by increases in urethral pressure, which may help mark territories with urine or milk urine through the urethra (Conte et al., 1991; Van Asselt et al., 1995). Other species may exhibit varying degrees of this milking response, but humans are not believed to exhibit it.

neither in female guinea pigs (Van Asselt et al., 1995) (Brading, 1999), who exhibit total suppression of EUS EMG activity during voiding (Figure 5b). It's interesting to note that duloxetine, which recently received European registration for the treatment of SUI, has been demonstrated to increase EUS EMG activity in response to bladder filling in cats and guinea pigs. This finding raises questions about the potential of EUS EMG activity to detect drug-induced changes in urethral function (Katofiasc et al., 2002).Pressure profile of the urethra Numerous techniques are used in both preclinical and clinical settings while doing profilometry. Animal models frequently use perfusion, balloon, or micro-tip type pressure transducers in preclinical profilometry research. These transducers can be static (Brune et al., 2001)—that is, the pressure transducer is positionedpull-through technique (maintained in situ to record resting pressure at one or more locations along the urethra) or both (Rosin et al., 1980). Pressure profilometry has been used to study urethral function in several species, including pigs (Bridgewater et al., 1993; Greenland et al., 1996), rats (Resplande et al., 2002), rabbits (Bodeker et al., 1975), cats (Gookin et al., 1996), and rabbits (Bodeker et al., 1996). Nonetheless, this method has been most frequently used with female dogs for drug effects (Brune et al., 2001; Buckner et al., 2002), canine incontinence diagnosis (Rosin & Barsanti, 1981; Richter & Ling, 1985; Gregory, 1994), and urethral function physiology (Watana-chote, 1982; Ali-El-Dein & Ghoneim, 2001). Specifically, research conducted on female canines using pull-through methods has not only describe the overall urethral pressure but also the locations that, when at rest, generate the highest pressure within the urethra and the regions that react to the administration of drugs, nerve stimulation, or pressure increases brought on by stress.

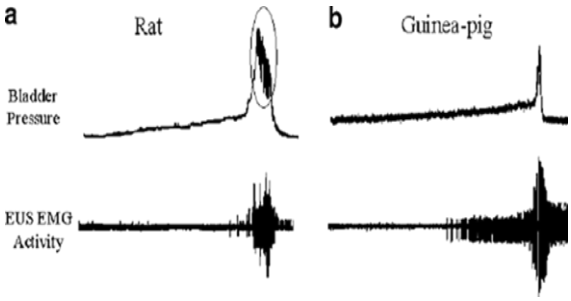

Figure 5 Normal saline cystometry in urethane-anaesthetised female CD rat and Dunkin Hartley guinea-pig. (a) In rat cystometry, bladder filling occurs as in other species; however, little EUS EMG activity does not appear to become active during the filling phase. Upon initiation of micturition, EUS EMG activity increases and high-frequency pressure oscillations become apparent in the bladder pressure trace (ringed). (b) With guinea-pig cystometry, bladder filling occurs as in the rat; however, as bladder volume increases, EUS EMG activity becomes apparent and slowly builds as bladder pressure increases. Upon micturition, EUS EMG activity is abolished and voiding occurs. Post void EUS EMG activity returns to promote urethral closure.

Urethral pressure profilometry Profilometry is carried out both clinically and preclinically using a number of different methodologies. Preclinical profilometry experiments in animal models tend to utilise perfusion, balloon or micro-tip type pressure transducers with either static (Brune et al., 2001) (i.e. the pressure transducer placed at a single or multiple points along the urethra and kept in place to record resting pressure) or pull-through methodology (Rosin et al., 1980). Urethral function in a number of species has been investigated using pressure profilometry, including rat (Resplande et al., 2002), rabbit (Bodeker et al., 1975), cat (Gookin et al., 1996) and pig (Bridgewater et al., 1993;

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Greenland et al., 1996). However, the most common utility for this technique has been in female dogs, in terms of drug effects (Brune et al., 2001; Buckner et al., 2002), diagnosis of canine incontinence (Rosin & Barsanti, 1981; Richter & Ling, 1985; Gregory, 1994) and in understanding the physiology of urethral function (Watana- chote, 1982; Ali-El-Dein & Ghoneim, 2001). In particular, studies in female dogs utilising pull-through methodology not only provide information with regard to overall urethral pressure but also define which regions produce maximum pressure within the urethra at rest and which regions respond upon drug administration, nerve stimulation or stress-induced pressure rises. Leak point pressure Leak point pressure again has been utilised both clinically (Khullar & Cardozo, 1998) and preclinically in a number of species (Brune et al., 2001; Buckner et al., 2002; Damaser et al., 2003). The methods utilised to induce leak in animal models can vary however, ranging from simply applying pressure to the abdomen with the palm of the hand in dogs (Brune et al., 2001) to placing rats on a tilt table with a pressure clamp (Chermansky et al., 2004) or utilising a blood pressure (BP) cuff (Rawlings et al., 2001). In all cases however, leak point pressure measurements are taken as the peak bladder pressure prior to leak, measured using a bladder cannula, which can also be used to fill the bladder prior to leak point measurement. Leak point pressure assays do have the advantage of being a dynamic test that directly evaluates the ability of the urethra to protect against leakage caused by increases in abdominal pressure and the potential of drugs to improve this ability. In a study comparing the measurement of urethral function using static and pull- through profilometry and leak point pressures in the dog, the authors concluded that all three methodologies provided useful information and were able to predict dose–effect relationships for a1A adrenoceptor agonist-induced effects on urethral function (Brune et al., 2001).

Retrograde perfusion or retro-resistance pressure Although both urethral pressure profilometry and leak point pressure measurements have been utilised clinically, they require an intraurethral cannula that then alters normal resting anatomy and sensation in the urethra. In addition, as they fail to discriminate the severity of incontinence between patients, a further methodology has been developed that applies an infusion of saline against the closed EUS. Urethral retrograde perfusion or retro-resistance pressure is defined as that pressure required to achieve and maintain an open urethral sphincter. Initial clinical investigations have shown that the technique can reliably differentiate between normal women and women with SUI and between severity of incontinence (Slack et al., 2004). Preclinically, little work has been carried out to determine the usefulness of retrograde perfusion in the measurement of drug effects in animals. Retrograde perfusion pressure measurements were found to be significantly reduced in rats that had undergone transabdominal- urethrolysis in comparison to control rats, suggesting the need for further investigation in a number of animal species (Rodriguez et al., 2005). Models of urethral dysfunction A number of animal models of urethral dysfunction have been explored in order to induce similar effects as seen in human SUI. These include pudendal nerve crush or transection (Damaser et al., 2003; Hijaz et al., 2005), vaginal distension or birth trauma (Bakircioglu et al., 2001; Kuo, 2002; Resplande et al., 2002; Damaser et al., 2003; Ferguson et al., 2005), electrocauterize- tion (Chermansky et al., 2004) and urethrolysis (Rodriguez et al., 2005). All these methodologies induce either nerve or muscle/ligament damage or both in order to reduce the function of the urethral continence mechanism. Measurements of urethral competency in these studies strongly suggest that continence mechanisms are impaired. Indeed, studies invest- gating the effect of sneezing on urethral function in normal rats and rats that have undergone urethral damage suggest that continence is impaired in these animals (Bakircioglu et al., 2001; Adachi et al., 2003; Damaser et al., 2003). Few studies at present have looked at drug-induced changes in urethral function in such models; however, a recent investigation of sneeze-induced incontinence in birth trauma rats has shown increased urethral function and continence after administration of the noradrenaline reuptake inhibitor litoxetine (Kaiho et al., 2005). Such results

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provide encouragement for further investigation. et al., 2005). Such results provide encouragement for further investigation. Animal models of sexual behaviour and function: general considerations

In recent years, our understanding of human sexual function and dysfunctions has grown. It is clear that sexual responses are complex, consisting of a number of coordinated psycho- logical and physiological mechanisms. Therefore, different in vivo models exist, focused on the neurobiology, psychophy- siology and different functional components of male and female sexual responses (for reviews on the pharmacology and physiology of sexual function, see Andersson, 2001; Munarriz et al., 2002). This section will briefly highlight some of the preclinical models that are commonly used in sexual function research and, where available, highlight clinical data where the animal models have been predictive of pharmacological activity in humans. The roles of hormones in sexual health, while crucial, are outside the scope of this review and will not be discussed.

Reproductive behaviours vary greatly across species. For example, sexually receptive female rats display short episodes of lordosis (see below) interspersed with running or darting away from the male, whereas female hamsters hold the lordosis posture for many minutes without movement. Similarly, males of some species perform multiple intromissions before ejaculation, while others hold an intromission (or lock) for many minutes before ejaculating. Therefore, before investigat- ing the effects of pharmacological agents on reproductive behaviours, it is important that the physical and temporal aspects of reproductive behaviours are established in the species of interest and can be robustly measured.

Studies should be designed to take into account the normal behaviour of the test animal, for example, whether it is diurnal, nocturnal or crepuscular. The laboratory conditions such as the duration of the light cycle can also influence the data generated. This is particularly important to seasonal breeders; for example, reproductive behaviours decline in male hamsters over a number of weeks if they are housed in day lengths shorter than 12.5 h of light per day due to declining testosterone levels brought about by testicular regression. The size and design of the test chamber can also influence the reproductive behaviours displayed. For example, female paced mating behaviour can only be studied when the test arena allows the female to escape from the male. In summary, the test conditions and experimental environment need to be carefully considered, as they can greatly influence the reproductive behaviours displayed (Cherry, 1993; Price, 1993; Meisel & Sachs, 1994).

When trying to understand how these preclinical models translate to humans, it should also be borne in mind that the primary purpose of sexual activity in animals is reproduction, while in humans it is predominantly recreational. The fact that animal sexual behaviors are highly stereotyped and species specific also makes translational interpretation to humans difficult. The translational interpretation of rat reproductive behaviors to man, including behaviors such as mounting, intromission latencies and lordosis quotients (LQ), which have no obvious equivalents in humans, has been and continues to be widely debated and reviewed (Sachs & Barfield, 1976; Dewsbury, 1979; Pfaus et al., 1990; 2003; Meisel & Sachs, 1994; Pfaus, 1996; Agmo et al., 2004).

Models of male sexual function: Erectile function Monitoring intracorneal pressure (ICP) is the most common method of preclinically monitoring the quality of an erectile response. ICP has been monitored in both conscious and anaesthetized animal models. The devel- opment of electronic data capture systems now allows various aspects of the ICP response to be measured (Figure 6). Typically measured endpoints include the basal ICP, peak ICP, plateau ICP, time to erection and detumescence time, duration of response, area under the ICP time response curve and the number of erections observed in a given time period. The aim is to use these end points to quantify the different phases and quality of the ICP response and the effect of the actions of drugs upon them. Anaesthetized animal models of male erectile dysfunction Nerve stimulation models: In anaesthetized animal models, measurement of ICP is usually performed by the insertion of a hypodermic needle into the body of the corpus cavernosum. The needle is attached to

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tubing, filled with heparinized saline and connected to a pressure transducer and data capture system. Additionally, systemic BP is monitored and data are usually expressed as a ratio of ICP/BP. This is because ICP is controlled by both penile vascular mechanisms and systemic hemodynamics, and a ratio of ICP over BP provides a measurement reflective of the penile component.

Stimulation of either the cavernous nerve or the pelvic plexus results in an increase in ICP (Rehman et al., 1998). Experiments to investigate the action of novel agents usually involve the selection of submaximal stimulatory frequencies and voltages to evoke an ICP response. The action of a novel agent on this submaximal response is then determined. Studies have been performed in both small and large animals (Carter et al., 1998; Vemulapalli et al., 2001; Ueno et al., 2002). Studies in larger animals such as the dog allow a more detailed investigation of both penile and systemic hemodynamics. Hence, the effects of a novel pharmacological agent on both erectile function and the cardiovascular system may be assessed at the same time in a single experimental animal.

Chemical-induced responses: The action of compounds and neurotransmitters on the penile vasculature can be investigated by infusing agents directly into the corpus cavernosum (Juenemann et al., 1986; Lin & Lin, 1996). Additionally, this technique can be used to stimulate biochemical pathways involved in the control of penile erection, for example, infusion of the nitric oxide donor sodium nitroprusside. The effect of compounds may then be tested on the activated biochemical pathway by monitoring the subsequent downstream functional effects on ICP (Carter et al., 1998).

Compounds and neurotransmitters may also be managed directly to their proposed site of action in the CNS, for example, using stereotaxic procedures to discrete regions of the brain by microinjection or to the spinal cord by intrathecal administration. Additionally, tool compounds and peptides that would not normally cross the blood–brain barrier may be used. These techniques have been successfully used to show that apomorphine has both a central site of action in the paraventricular nucleus (PVN) (Melis et al., 1987) and a spinal location of action that is pro-erectile (Giuliano et al., 2002). The spinal involvement of oxytocin in penile erection was established using intrathecal infusion of this neurotransmitter (Giuliano et al., 2001b).

Central nervous system electrical stimulation: The CNS can also be stimulated to cause erectile reactions. Differential brain regions are electrically activated and peripheral genital responses (such as genital muscle activation or peripheral nerve recordings) are observed through the use of stereotaxic methods.

The hypothalamus, and specifically the PVN and the medial preoptic area (MPOA), is the most often studied region of the central nervous system (CNS) involved in the regulation of sexual behavior. ICP rises in response to electrical stimulation of these regions (Giuliano et al., 1996; Chen et al., 1997).

Reproductive behaviors of male rats: The rat is the most frequently utilized animal in research on male sexual behavior. The complicated set of synchronized motor behaviors and reflexes that make up male rat reproductive behavior. The first sexual behavior a male rat exhibits toward a female is typically an anogenital examination. A series of mounts and intromissions come next. When a male rat mounts a female, he does it from behind and grabs her by the flanks with his front foot. When a male mounts and successfully penetrates the vagina, it is known as an intromission. Male rats mount and intromit many times during copulation. The male often dismounts from the female after a mount or intromission. The man ejaculates after a sequence (or bout) of intromissions. Ejaculation is easy to recognize. by an extended intromission, frequently accompanied by deeper thrusting and a delayed withdrawal into a "crucifix" position after ejaculation. After ejaculating, the man usually grooms his genitalia, stops interacting sexually with the woman for a few minutes, and makes high-pitched ultrasonic noises. It is simple to identify the experimental rat's copulatory behavior by counting the number of mounts, intromissions, and ejaculations within a certain time frame, as well as other experimental endpoints including the time of the first mount, intromission, and ejaculation.

Models of male erectile dysfunction that are conscious The following experimental behavioural

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paradigms are frequently used to evaluate pharmaceutical agents: a male animal in isolation, a male animal in the presence of a female animal during oestrus and copulation, but without access to her Erections produced by compounds: Rats without access to female animals are given the test substance, and the animal is watched to see if it causes an erection. These studies have been utilized to find erection-inducing drugs, including PT-141 (Molinoff et al., 2003), melanotan II (MT-II) (Giuliano et al., 2005), and apomorphine (Bernabe et al., 1999). The sheer act of handling a rat (dosing, for example) might cause spontaneous erections in the test animal, hence caution must be used when planning such tests and include suitable experimental time-matched controls.

Non-contact erections: Placing a male animal in oestrus next to a female animal will cause a non-contact erection (Sachs et al., 1994). Usually, this is accomplished via putting a male animal in one side of a cage or observation area (typically a rat). A female rat in oestrus, or an ovariectomized female rat placed in a behavioral oestrous state with the administration of progesterone and estrogen, is placed in the opposite half. The cage is divided in half by a perforated separating wall.

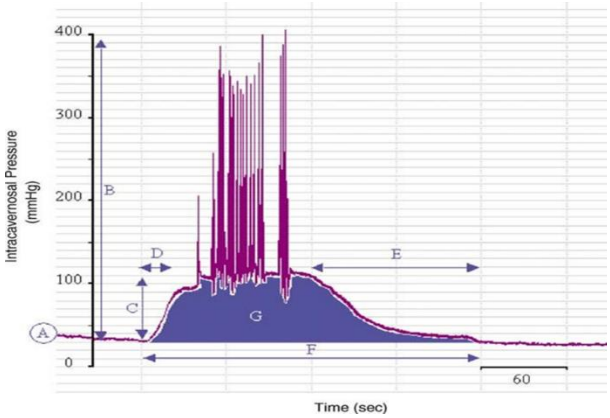

Figure 6 An apomorphine-induced rat penile erection ICP trace. An example of an apomorphine-induced rat penile erection trace recorded using radiotelemetric equipment is shown. Typical measurements include (A) basal ICP, (B) peak ICP, (C) plateau ICP, (D) time to erection, (E) detumescence time, (F) duration of response and (G) area under ICP time response curve.

or observation chamber. The dividing wall allows the passage of auditory, visual and pheromonal cues between the two animals. The number of erections or if the animal is telemetered its ICP response is monitored over a given period. As a non-contact evoked erection is dependent on visual, olfactory and auditory cues from the female and not (due to separation by a barrier) due to tactile reflexive mechanisms, the response is believed to be primarily under the influence of forebrain regions of the brain. Male rats with lesions to the MPOA of the hypothalamus show normal non-contact erectile responses and reduced copulatory behaviour (Liu et al., 1997). It has been postulated that the frequency of non-contact erections (alternatively called female-enhanced spontaneous erections) is an indicator of sexual arousal (Sach, 2000).

These studies may be used to identify agents that are facilitators of erectile function. Facilitators are agents that initiate minimal or no erectile responses in their own right, but enhance erectile responses generated by a pro-erectile agent in the presence of a female animal in oestrus (Anderson et al., 1999).

Copulation studies: Copulation studies and the associated end point measures described are routinely used to define the sexual behavior of a test animal and the effect of a pharmacological agent upon it, or alternatively to phenotype profile genetically modified animals. These types of studies offer the most comprehensive way of evaluating sexual function in a normal behavioral context. However, as various factors can influence copulatory behavior, such as inspiration, locomotion and the behavioral status/sexual experience of the partner animal, it is difficult to accurately identify the effect of a pharmacological agent on a single physiology such as erection. While end point measures such as the intromission ratio (intromission ratio number of intromissions/(number of intromissions number of mounts)) are commonly used as an indicator of erectile function, any observed differences should be followed up with confirmatory experiments using more robust experimental measures such as ICP dimensions.

Telemetric recording ICP may be measured in conscious rats using radio telemetric techniques

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(Figure 6) (Bernabe et al., 1999). Following the washout of a test drug, rats may be re- tested with a second dose of the test drug or an alternative agent. Thus, telemetered animals allow the use of statistically robust crossover experimental designs, reducing experimental variability and ultimately the number of test animals. Instrumented rats may be monitored intermittently over many months and therefore the effect of age on the quality of the ICP response (and the development of erectile dysfunction) can be monitored. Additionally, the choice of inbred rat strain to be implanted with the telemetric device (e.g. the diabetic Zucker fa/fa rat) and/or experimental manipulation (e.g. induction of dietary-induced hypercholesterolemia) to mimic the disease situation can further refine the experimental model.

Cavernous nerve injury model The incidence of erectile dysfunction increases following pelvic surgery, in particular following radical prostatectomy, due to damage of the cavernous nerves. In the cavernous nerve injury model (CNI), the cavernous nerves are either unilaterally or bilaterally sectioned or damaged to impair erectile function. The unilateral CNI model has been used to investigate mechanisms and potential pharmacological and gene therapy treatments associated with nerve regeneration. The bilateral model has been used to investigate the pathological condition and is believed to mimic the condition in humans following radical prostatectomy. It has been used to explore the actions of growth hormones and potential gene therapy approaches (Jung et al., 1998; Bakircioglu et al., 2001; Chen et al., 2005).

Models of ejaculation Ejaculation is a highly complex, tightly coordinated series of reflexes and mechanisms. Owing to its complexity, ejaculation is very difficult to study experimentally. No preclinical model currently exists in which all components are present and measurable. In recent years, there has been an increase in our knowledge of the neuroanatomical pathways that control ejaculation within the brain (Pfaus & Heeb, 1997; Veening & Coolen, 1998) and the spinal cord (Truitt & Coolen, 2002; Truitt et al., 2003).

Behavioural ejaculation can be identified in experimental animals. The majority of studies on premature or retarded ejaculation have been undertaken in rats with normal sexual behaviour. Recently, it has been shown that within a rat population there exists a subgroup of fast ejaculators and a subgroup of slow ejaculators, each representing approximately 10% of the population at each end of a Gaussian distribution. It has been postulated that these subpopulations are compar- able to variations seen in ejaculatory times in the human population (Waldinger et al., 2005a), with the faster ejaculat- ing subset representing a model of premature ejaculation and the slower ejaculating rats representing a model of retarded (an)ejaculation (Waldinger & Olivier, 2005).

A variety of pharmacological agents have been shown to modify sexual behaviour in rats and postulated a role for several neurotransmitters (Bitran & Hull, 1987) and neuro- peptides (Argiolas, 1999). 5-HT1A and 5-HT2C receptors are known to control the speed of ejaculation in rats. Activation of 5-HT1A receptors shorten the ejaculation latency time and activation of 5-HT2C receptors delays ejaculation (Ahlenius et al., 1981).

Urogenital reflex as a model of orgasm in both male and female rats The urogenital reflex (UG reflex) model may be used to study both penile erection and ejaculatory reflexes. In urethane-anaesthetised, acutely spinalised (or brain lesioned) rats, complex coordinated sexual responses may be elicited by urethral distension. In male rats, the elicited response, known as the UG reflex, consists of colonic contractions of the perineal muscles, rhythmic firing of the cavernous nerve, penile erections and ejaculation (Chung et al., 1988; McKenna et al., 1991). The perineal muscles are all activated simultaneously, as occurs in humans at the point of sexual climax (Petersen & Stener, 1970). The paraigoantocellular reticular nucleus in the brainstem is the main source of descending inhibitory control over the spinal sexual reflexes (Marson & Mckenna, 1990). If this region of the brain is lesioned, the inhibitory control is removed and the UG reflex can be evoked in spinally intact animals. The UG reflex may also be evoked in non-spinalised animals by bilateral stimulation of the MPOA (Marson & Mckenna, 1994). This model has predominantly been used to investigate the

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identification of spinal ejaculatory pattern generators and the supraspinal control of sexual reflexes. Models of female sexual function

Anaesthetised animal models Nerve stimulation models: Stimulation of the pelvic nerve in anaesthetised female rats (Vachon et al., 2000; Giuliano et al., 2001a) and rabbits (Munarriz et al., 2003) has been shown to increase vaginal blood flow, clitoral ICP, vaginal wall pressure, vaginal length and blood flow, and decreases vaginal luminal pressure. The effect of pharmacological agents on these end points, which are used as an index of sexual arousal, has been investigated (Min et al., 2000). As women have been reported to experience cyclic fluctuations in sexual arousal and desire that coincide with ovulation and female rats display increased behavioural sexual activity, which coincides with the periovulatory period of their oestrus cycle, it is clear that a knowledge of the hormonal status of the animals is key to the interpretation of results. Commonly, ovariectomised animals are used and hormones (oestrogen and progesterone) are administered to establish the level of oestrus required in the experiment.

The development of female models of peripheral arousal has been hindered by the identification of robust end-point measures. Vaginal and clitoral blood flow is commonly measured in anaesthetised animals using laser Doppler flow probes. The identification of robust preclinical and clinical end-point measures of female genital arousal is required. Chemical-induced models and electrical stimulation of the CNS: The techniques described for males above may also be utilised in female models. Female rat reproductive behaviours The motivation or desire for an animal to engage in a sexual encounter and its ability to physically consummate are separate components of reproductive behaviours. Rats display two distinct patterns of behaviour: motivational, proceptive or solicitous behaviours and receptive or consummatory behaviours. These two distinct components of sexual behaviour, motivation and consummation, have been shown in male rats to be mediated by different brain mechanisms (Everitt, 1990).

Female proceptive behaviours include behaviours such as ‘hopping’, ‘darting’ and ‘ear wiggling’ that serve to gain the attention of the male rat and initiate sexual activity. Receptive behaviours include the commonly reported reflex posture of lordosis (see below). Sexually receptive female rats display short episodes of lordosis interspersed with running or darting away from the male. This is known as ‘paced’ mating behaviour, which has been shown to be more sexually rewarding than ‘non-paced’ mating behaviour (Paredes & Vazquez, 1999).

Experimental procedures have been established for assessing female proceptive behaviours (Beach, 1976). In the past, this has been achieved experimentally by physically restraining the sexually active male in a number of ways (Meyerson & Lindstrom, 1973; Edwards & Pfeifle, 1983); however, more ethological models have now been developed, which allow ‘paced’ mating behaviour to be displayed.

Lordosis is the reflex posture that a sexually receptive female rat adopts in response to appropriate tactile stimulation, such as an attempted mount by a male rat or pressure on the back, flanks or anogenital region. The lordosis posture is characterised by pronounced arching of the back, with the head and hindquarters elevated, back feet extended and tail deflected to one side.

Proceptivity model: The proceptivity model consists of a large circular open field with two diametrically opposed chambers on its outer circumference. The sidewall of each chamber faces into the arena and consists of a holed Perspex wall or grill. A single stimulus animal is placed in each outer chamber and a single test animal is placed into the open-field arena. The amount of time the test animal spends actively seeking each stimulus animal, or the amount of time spent in a designated area next to each stimulus animal, is measured. The holed Perspex wall or grill allows visual, olfactory and auditory cues to pass from the stimulus animals into the open-field arena, but prevents direct contact. The sex, hormonal status and sexual experience of the test and stimulus animals can be varied depending on the purpose of the experiment. For example, the effect of a drug on female sexual motivation could be investigated by placing a sexually active male rat in one chamber and a castrated male rat in the other. The drug-treated

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female rat would then be placed in the open-field arena and monitored. This model has been used to investigate sexual incentive motivation in male (Hetta & Meyerson, 1978) and female (Meyerson & Lindstrom, 1973; Agmo et al., 2004) rats.

Bilevel chambers: Bilevel chambers are behavioural observa- tion chambers that contain two levels connected together by ramps or ladders. These chambers may be used to explore the proceptive behaviours of both male and female animals. Normal female rat reproductive behaviours involve solicita- tions by the female rat, which results in the male mounting the female and intromission. Following intromission, the female rat will run away and eventually stop and adopt a lordosis posture in order to allow the male to mount and intromit a further time. This process known as pacing will continue until the rat ejaculates. The number of level changes is believed to give an indication of sexual motivation. Copulation studies performed in these chambers have shown that female hormonally primed ovariectomised rats level change signifi- cantly more than non-hormonally primed rats (Mendelson & Gorzalka, 1987). Male rats show an increased amount of level changing when in the presence of an oestrus compared to an anoestrus female rat (Mendelson & Pfaus, 1989), and additionally the amount of level changing decreases following ejaculation (van Furth & van Ree, 1996). Pharmacological studies have included the investigation of the mixed MCR3 and MCR4 agonist PT-141 (Pfaus et al., 2004). Currently, there is debate on whether bilevel chambers allow true sexual pacing, as the female rat can only run away and not escape from the male rat (Agmo et al., 2004).

Escape or unilevel pacing chambers: Escape or pacing chambers consist of behavioural observation chambers that are divided into two by a central vertical divider. The bottom of the divider has a number of holes cut into it that are large enough to allow the female rat to pass between the two chambers but small enough to restrict the male rat to one of the chambers. Thus, the female can 'escape' from the male and by doing so control or 'pace' copulation (Paredes & Vazquez, 1999). Pharmacological studies have included investigation of PT-141 (Pfaus et al., 2004) and the actions of 5-HT2A and 5-HT2C agonists (Nedergaard et al., 2004) on proceptive sexual behaviours.

Lordosis model: Owing to its ease of identification, lordosis is one of the most widely investigated reflexes in sexual health research (Pfaff & Schwartz-Giblin, 1988). The lordosis reflex is Depending on the levels of progesterone and estrogen. Only a mild stimulation of the reflex is produced by oestrogen treatment alone. However, it has been demonstrated that medications that bind to oxytocin, opioid, adrenoceptor, dopamine receptor, or GABA receptors in specific hypothalamic brain regions promote lordosis in ovariectomized rats treated with oestrogen alone (Kow et al., 1994; Pfaff, 2001).

The most often used technique to determine the degree of lordosis is called LQ, which divides the frequency of lordosis by a certain number of mounts, typically 10. For instance, LQ 100 is the ratio of adopted lordosis postures to attempted mounts. The lordosis model measures receptive behaviors and illustrates how they differ from preceptive (or desiring) behaviors. the capacity to carry out the physical actions needed for copulation.

Translation of pharmacology from animals to humans

A number of distinct molecular classes that have shown effective in treating erectile dysfunction or premature ejaculation in people have also produced some degree of success in animal models.

The effects of sildenafil and other phosphodiesterase type 5 (PDE5) inhibitors have been extensively studied and shown to be positively correlated in preclinical anesthetized animal models (Carter et al., 1998) and humans (Eardley et al., 2002). Specifically, the preferred model for determining the relative potency of PDE5 inhibitors is the anesthetized dog ICP model. Clinical Rigi scan investigations and phase II outpatient trials yield results that are predictive of the dog model, according to pharmacokinetic and pharmacodynamic modeling. The apomorphine Subcutaneous administration of a combined D1 and D2 receptor agonist causes penile erections in both men and constipated rats (Melis et al., 1987; Lal et al., 1987). This drug is thought to act in the PVN based on microinjection experiments (Melis &

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Argiolas, 1997; Sato et al., 1999; Adachi et al., 2003). Additionally, the possibility of a spinal mode of action is suggested by intrathecal injection (Giuliano et al., 2002). On the other hand, it has been demonstrated that the dopamine antagonist haloperidol lowers sexual arousal in both rats and humans (Pfaus & Phillips, 1989; Petrie, 1985). Alpha-2 adrenoceptor antagonist yohimbine has shown some efficacy in both people and animals. Although there are alpha-2 adrenoceptors in both the central and peripheral regions, it is still unknown where yohimbine's pro-erectile activity takes place. (MT-II) Melanotan II is a Alpha-melanocyte-stimulating hormone (a-MSH) has a synthetic, non-selective counterpart. Melanocortins have been linked to the control of sexual behavior, such as penile erection, sexual motivation, and the preputial gland's release of sexual attractants in female rats (Thody et al., 1981). In a rabbit model, it has been demonstrated that MT-II raises ICP (Vemulapalli et al., 2001). It has been observed that MT-II can cause an increase in sexual desire and can start a penile erection in men with psychogenic (Wessells et al., 1998) and organic erectile dysfunction (Dorr et al., 1996) as well as normal individuals. Overall, strategies that enhance sexual function in humans and male animals seem to be reasonably correlated.

Premature ejaculation does not yet have a treatment that has been approved by a regulatory body. The use of off-label pharmaceutical medicines entails SSRIs (serotonin reuptake inhibitors; paroxetine, sertraline, fluoxetine), PDE-5 inhibitors, and topical local anesthetics (e.g., lidocaine). Since SSRIs have been evaluated in rat sexual behavior models (Mos et al., 1999; Waldinger et al., 2002) and humans (Waldinger et al., 2002; 2004; 2005b), both acutely and chronically, they are of particular interest. Regarding how SSRIs work, there seems to be a good correlation between preclinical and clinical research. Rat and human ejaculatory parameters are affected by acute non-sedative SSRI administrations, however prolonged treatment further postpones ejaculation (Cantor et al., 1999). Additionally, it has been demonstrated that acute alcohol intoxication delays ejaculation in rats (Dewsbury, 1967; Pinel et al., 1992) as well as men (Malatesta et al., 1979).

IN CONCLUSION:

The LUT and sexual function have been the subject of increased study activity in recent years, with a focus on developing new medications to address the symptoms of both disorders. This is partially because pharmaceuticals have been developed to treat OAB, BPH, male erectile dysfunction, and the annoying symptoms that compel those who suffer from these disorders to seek therapy. people. Our knowledge of the peripheral and central regulation of the LUT and male erection control has significantly advanced within the past ten years. Nonetheless, our knowledge of the central nervous system's involvement in both male and female sexual activity, as well as the peripheral regulation of female genital blood flow, is still lacking. We will have to wait for comprehensive clinical evaluation of novel mechanisms in clinical trials before we can better grasp the relationship between therapeutic benefit in humans and animal models of urological function.

Studies on humans and animals have led to the current understanding of the physiological, pharmacological, and psychological factors governing sexual function and the LUT. Preclinical models and clinical data are starting to correlate, which will improve the current animal models and should boost their capacity to forecast clinical efficacy in people. Our knowledge of the peripheral and central regulation of the LUT and male erection control has significantly advanced within the past ten years. Nonetheless, our knowledge of the central nervous system's involvement in both male and female sexual activity, as well as the peripheral regulation of female genital blood flow, is still lacking. We will have to wait for comprehensive clinical evaluation of novel mechanisms in clinical trials before we can better grasp the relationship between therapeutic benefit in humans and animal models of urological function.

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