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Kevin T. McVary *Editor*

Contemporary Treatment of Erectile Dysfunction

A Clinical Guide

Humana Press

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Preface

Erectile dysfunction (ED) was once considered psychogenic in origin and frequently neglected by healthcare providers. More recently, there is increasing recognition of its many physiological causes, its impact on the quality of life, and the potential for therapy to improve the quality of life, self-esteem, and the ability to maintain intimate relationships. Despite these important steps forward, the pathophysiology of ED remains incompletely understood.

This book represents the current state-of-the-art in the evaluation, diagnosis, and the treatment of this important and common global problem. The contributing authors represent the world's most experienced, knowledgeable, and most expressive investigators in the field and are able to update the reader on the current aspects of the clinical problem as well as the state-of-the-art in evaluation, pathophysiology, hormonal evaluation, oral and local therapies, psychotherapy, prosthetics, and areas of uncertainty pertaining to ED.

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Chapter 1
Animal Models for the Study of Erectile Function and Dysfunction

Kevin E. McKenna

Abstract The mechanisms of penile erection have been investigated using animal models from the beginning of modern investigative physiology. In 1863, Eckhard reported that electrical stimulation of the nervi erigentes (pelvic nerves) induced penile erection in the anesthetized dog. This study identified that erection is a vasodilatory event. Over 125 years of animal experimentation passed before the vasodilatory neurotransmitter was identified as nitric oxide. Now, due largely to the use of animal models, the hemodynamics, molecular biology, and neurobiology of penile erection are understood in their broad outline. Recent animal research has concentrated on identifying the mechanisms of erectile dysfunction (ED) in a variety of pathophysiological states.

Keywords Pelvic nerves • Sexual function • Erectile physiology and pathophysiology • Cardiovascular disease • Nonhuman primate erectile mechanisms • Rodent biology

Introduction

The mechanisms of penile erection have been investigated using animal models from the beginning of modern investigative physiology. In 1863, Eckhard [1] reported that electrical stimulation of the nervi erigentes (pelvic nerves) induced penile erection in the anesthetized dog. This study identified that erection is a vasodilatory event. Over 125 years of animal experimentation passed before the vasodilatory neurotransmitter was identified as nitric oxide. Now, due largely to the use of animal models, the hemodynamics, molecular biology, and neurobiology of penile erection are understood in their broad outline. Recent animal research has concentrated on identifying the mechanisms of erectile dysfunction (ED) in a variety of pathophysiological states. One clear finding of these studies, since verified in human studies, is that the neural, endothelial, and smooth muscle defects which underlie erectile dysfunction, represent a powerful warning of the probability of developing serious cardiovascular disease. This is because the mechanisms regulating the vascular tissue of the penis are essentially the same in most other vascular beds. Thus, the animal models developed for the study of penile erection provide a useful tool for investigating the early cardiovascular effects of diabetes, obesity, diet, aging, etc.

Research in the area of sexual function critically depends on research models. Investigations into the anatomy, physiology, cell biology, biochemistry, and pharmacology of sexual function are necessary to develop new therapies for the treatment of human disease. It is especially important that researchers choosing to adopt an experimental approach be aware that any given model has strengths and limitations. No animal model can ever represent all aspects of human

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physiology and pathophysiology. Therefore, all animal models require a series of compromises on the part of the investigator. Several factors must be considered in the choice of a particular model. Researchers must consider whether the function being investigated is similar in the animal model and the human, the strength of the literature of that function in that species, the technical feasibility of the model, and cost. For example, hemodynamic studies often require larger species for purely technical reasons. Nonhuman primate erectile mechanisms and sexual behavior may more closely model the human. However, cost and animal welfare considerations present major barriers to the widespread use of nonhuman primate models. Rodent models are the most commonly used, largely driven by practical concerns and the huge literature on rodent biology. An essential point is that a very rich literature of studies of erectile function in monkeys, dogs, cats, rabbits, rats, mice, and other species demonstrate that physiology and neural control of penile erection is highly conserved in mammals. Further, results from these animal studies have been remarkably successful in providing insight into human erectile physiology and pathophysiology, which is the true measure of all animal research models.

Models Used in the Study of Penile Erection

Electrical Stimulation of Peripheral Nerves

The first model for the study of penile erection, and still an important model used today, is the electrical stimulation of peripheral nerves in anesthetized animals and examination of resulting changes in the penis. Early experiments by Eckhard, Goltz, Gaskell, and Langley performed in either dogs, cats, or rabbits [2] showed that electrical stimulation of sacral nerves, anterior sacral roots, or the lumbosacral spinal cord (i.e., activation of parasympathetic pathways) elicited penile erection. Electrical activation of sympathetic pathways was antierectile. Simultaneous stimulation of parasympathetic and somatic nerves increased the erectile response [3]. Further refinements of the method came with measurements of penile size by plethysmography in response to peripheral nerve stimulation and systemically injected drugs in rabbits [4].

This work has been extended by more extensive hemodynamic measurements [5–7]. These studies required the use of large animals, anesthetized dogs, and monkeys. Parasympathetic stimulation caused a transient arterial blood flow increase in the internal pudendal artery, followed by a sustained increase in intracavernous pressure (ICP). This increase in ICP was converted to suprasystolic ICP levels when combined with pudendal nerve stimulation.

Pressure Recording in the Corpus Cavernosum

Direct measurement of ICP provides the most reliable and quantitative response of the penis to peripheral and CNS neural activation. In addition, intracavernous injections of a variety of agents can be used to identify the cellular and molecular mechanisms of the erectile process. Measurement of ICP is typically performed by inserting a hypodermic needle into the body or the crus of the corpus cavernosum. The needle is connected to tubing filled with heparinized saline to prevent clotting. The tubing is attached to a calibrated strain gauge whose output is fed to computerized data acquisition systems. In the absence of striated muscle contraction, the maximal ICP is systolic blood pressure (BP). That is, systemic blood pressure is the driving force for ICP. Changes in BP may induce changes in ICP, and could be wrongly interpreted as changes in penile function. For greatest accuracy, systemic blood pressure (BP) is usually measured, and the changes in penile function are expressed as the ratio of ICP/BP. In addition to measuring maximal ICP, the duration and amplitude of increases in ICP during an erectile response, rate of increase or decrease in ICP during tumescence and detumescence, and area under the ICP curve,

are all measures used to quantify the aspects of erectile function [8]. For pharmacological studies, a common approach is to construct a curve of the peak ICP/BP ratio achieved at either different stimulation frequencies or intensities. A change of this curve indicates the effect of pharmacological agents on penile erections. Results from the studies of peripheral efferent and afferent nerve stimulation and the modulation of inter- or intracellular signaling pathways have been reviewed and provide clear demonstration of the utility of this model [9].

The majority of such studies have been performed in rats, largely for practical reasons, such as cost, maintenance and handling, and for the fact that the results have been shown to be clinically relevant. Another advantage of the rat is that vasodilatory parasympathetic input to the penis is conveyed by a single, easily identified nerve, the cavernous nerve, which facilitates electrical stimulation. These techniques can be adapted for use in mice, to allow the study of erectile function using molecular or gene-based techniques [10–12].

The search for the agent(s) responsible for penile vasodilation has been an extremely active area from the beginning of the study of erectile function. The models typically used have been electrical stimulation of penile efferents in anesthetized animals combined with systemic or intracavernous injection of drugs. Attempts were made to block stimulation-induced erection with antagonists and mimic it with agonists. Numerous candidates were investigated until nitric oxide (NO) was identified as the primary vasodilator messenger, using animal models [13–15]. This discovery was responsible for the introduction of phosphodiesterase type 5 (PDE5) inhibitors for the treatment of erectile dysfunction.

Vascular Smooth Muscle Cells In Vitro as a Model System in Erectile Research

Tissue culture of smooth muscle cells from the corpus cavernosum have been used to investigate a variety of cellular and molecular mechanisms relevant to erectile function. Cell culture offers numerous advantages over in vivo studies, such as the ability to precisely manipulate the environment, single cell imaging, characterizing ion channel and gap junction function, and transfection of cells for molecular studies. But, it is important to recognize that removing the cells away from their in vivo environment may significantly alter their biology due to the loss of the three dimensional architecture, and influences from other cells types, such as endothelial cells, and the loss of neural innervation. Thus, interpretation of findings must reflect an understanding of the balance between the advantages and disadvantages of the methodology.

Tissue culture techniques using penile tissue have been used to characterize the role of gap junctions between smooth muscle cells [16–18], potassium channels [19, 20], second messenger signaling pathways [21–23], and the mechanism of action of a variety of vasoactive agents [24–27].

Reflex Erection Elicited by Peripheral Sensory Stimulation

An early report indicated that sensory nerve stimulation did not induce reflex erection in cats deeply anesthetized with barbiturates [28]. More recent studies made use of the recognition that spinal sexual reflexes are under a tonic inhibitory control from supraspinal sites. Thus, following acute spinal section, genital sensory stimulation is effective in eliciting penile erection in anesthetized rats [29–32]. Stimulation of the dorsal nerve of the penis in acutely spinalized, anesthetized rats reliably elicits increases in intracavernous pressure, which may reach systolic pressure, indicating a full penile vasodilation [31, 32]. In some cases, concomitant perineal muscle contractions are observed, leading to suprasystolic ICP and full rigid erections. This technique is useful for the study of spinal reflex mechanisms and pharmacology.

The tonic descending inhibition of sexual reflexes arises from supraspinal sites and projects to the lumbosacral reflex centers [33, 34]. The anatomic site responsible for the inhibition has been identified in the rostral pole of the

paragigantocellular reticular nucleus, bilaterally located in the oblongata [35]. This area directly projects to pudendal motoneurons and interneuronal areas of the lumbosacral cord. Transection of the spinal cord facilitates spinal erectile reflexes by removing this descending inhibition. Obviously, spinal transection precludes the examination of supraspinal mechanisms controlling sexual responses. Experimental design requires careful consideration of these factors.

Urethrogenital Reflex

Sexual reflexes can be elicited in anesthetized male and female rats [30]. In urethane anesthetized, acutely spinalized rats, complex sexual responses can be elicited by a variety of pelvic stimuli, including the stimulation of the dorsal nerve of the penis. It was shown that urethral distension is a quantitative and highly reproducible stimulus. Hence, this response has been referred to as the urethrogenital (UG) reflex. In male rats, the UG reflex consists of rhythmic contractions of the perineal muscles, rhythmic firing in the cavernous nerve, rigid penile erections, and ejaculation. While this reflex includes penile erection, this model is now viewed primarily as a technique for investigating the expulsive phase of ejaculation. The perineal muscles are activated simultaneously in a series of rhythmic contractions, which are similar to those seen in human climax [36, 37], and in rats during copulation [38].

Penile Erection in Conscious Animals

Ex Copula Erections

The *ex copula* model was a commonly used unanesthetized rat model of erection; however, it has fallen out of favor in recent years due to its limitations [39, 40]. The rat is lightly restrained in a supine position, and the penis is retracted from the sheath. Relatively predictable "spontaneous" penile erections are thus elicited. The effects of drugs administered into the CNS and CNS lesions have been examined in this model. It has the advantage in that it does not involve social interaction with the female and it examines penile reactions directly. However, the rats must be trained before if they are to stop struggling during the testing, and invasive measurements of neural activity or hemodynamics are not easily performed. Furthermore, the stimuli eliciting these erectile responses are unclear.

Noncontact Erections

Noncontact erection (NCE) is a centrally generated erection model in conscious rats. Pigmented strains of male rats develop penile erections in response to the presence of estrous female even when physical contact is prevented [41]. Volatile odors from the estrous females have been shown to be the necessary and sufficient stimulus for this response [42]. Note that this response is mediated by the vomeronasal organ and the accessory olfactory system (pathways for the processing of pheromone stimuli), not the main olfactory system responsible for the sense of smell. This model is the first in which erections are generated by environmental sexual stimuli, without genital stimulation, possibly similar to psychogenic erections in the human. However, there is little evidence that pheromonal cues play any significant role in sexual arousal in humans. Thus, it is likely that NCEs in rats and psychogenic erections in humans are mediated by very different forebrain sensory mechanisms. Nonetheless, this is a model of a physiologically relevant, CNS-driven erection in unanesthetized animals, without the confounding complex social and sensory stimuli of copulatory behavior.

Erection Induced by Electrical and Chemical Stimulation of CNS Structures

A large number of studies have investigated the central control of penile erection using

precisely localized electrical or pharmacological stimulation, in both anesthetized and unanesthetized rats. Conversely, electrical or chemical lesions of specific brain nuclei have also been used. Typically, these studies involve the electrolytic destruction of brain sites under anesthesia. After several days of recovery, the animals are tested in behavioral situations. The vast majority of our current knowledge of CNS mechanisms are derived from a combination of these methods.

Typical procedures for these studies use anesthetized rats. However, it is possible to use this technique in awake, behaving animals. Under anesthesia, the animal's head is mounted in a stereotaxic frame that provides a coordinate system to locate specific brain areas. Small holes are drilled into the skull for the placement of electrodes for electrical stimulation, micropipettes, or hypodermic tubing for the administration of drugs. Physiological recordings of ICP and blood pressure are taken during the stimulation. In addition, recordings of peripheral nerve, skeletal muscle activation, or other physiological responses may be performed. Following the end of the experiment, the brain is removed and sectioned for histological verification of stimulation sites. For the administration of precise quantities of drugs, experimenters have used microliter syringes. These can be mounted directly in the stereotaxic microdrive and inserted into the brain, or be connected by tubing to an implanted hypodermic needle. The latter method allows the use of precise syringe pumps for continuous infusion. Another method is to use micropipettes filled with the drug solution. The drug is injected into the brain by attaching tubing to the end of the micropipette and applying precise pulses of pressurized nitrogen. Visualization of the fluid level in the micropipette with a calibrated microscope allows precise injection volumes in the low nanoliter range [43]. Similar methods can be used in awake, behaving animals. The hypodermic needle or micropipette is inserted under anesthesia as described. It is then glued in place to the skull with dental acrylic. After a suitable recovery period, tubing is attached to the needle or micropipette and connected to a syringe or pressure device outside the cage. In this way, the effects of drugs on behavior can be examined. Electrodes for electrical stimulation can be similarly implanted for later use in conscious animals.

Implantation of telemetric pressure recording devices can be combined with these techniques to allow precise measurement of ICP to electrical or pharmacological stimulation in conscious and freely moving conditions [8, 44]. Telemetric methods can also be used in copulatory studies, *ex copula* studies, and to study sleep-related erections [45].

A variation of the microinjection technique is intrathecal delivery. A fine catheter is threaded down the spinal column until the tip reaches the target spinal segment. The experiment can then be performed immediately, or the catheter can be secured by suture or cement and the animal allowed to recover from anesthesia and surgery for use in awake, behaving experiments. Many previous studies have suggested the importance of spinal control on modulating penile erection and sexual behaviors. For example, studies involving the intrathecal administration of oxytocinergic agents have identified a spinal proerectile role for this neurotransmitter [46, 47]. Such studies demonstrate that intrathecal administration is a useful tool for the investigation of spinal control erectile function.

Models of Erectile Dysfunction

A wide variety of pathophysiological models of ED have been proposed aiming to mimic the numerous pathological conditions responsible for ED in humans. The most common of these models are hypertensive rats, atherosclerotic rabbits, diabetic rats and rabbits, aged rats, castrated rats, and cavernous nerve-injured rats. Our understanding about the molecular mechanisms involved in the physiology of penile erection has advanced significantly in the last decade as a direct result of the use of animal models to study aberrant erectile mechanisms in various pathological situations. The purpose of this subchapter is to evaluate experimental disease animal models used to study ED and further our understanding

of species choice and end points associated with each animal model. These models have undoubtedly been useful, but caution must be observed on how closely they mimic human conditions.

Hypertension

Erectile dysfunction and hypertension are widely acknowledged to be associated, but there have been relatively few experimental investigations into the mechanisms. The animal model of hypertension most widely used to assess erectile function is the spontaneously hypertensive rat (SHR) [48]. A small number of investigations have also assessed the impact of secondary hypertension due to DOCA-salt treatment, aortoiliac balloon injury, experimental passive cigarette smoke inhalation, and increased alcohol consumption. In normotensive rats, these manipulations induced both hypertension and erectile dysfunction [49–52]. However, there remains considerable work remaining, linking the hypertension with specific pathologic derangements of the erectile microanatomy, cellular physiology, and molecular biology.

Aging

The development of ED with aging was first identified in copulatory studies [53, 54]. Subsequent studies using other models of erectile function discussed above, indicates that the ED in aged rats is due to the loss of smooth muscle and endothelium, fibrosis and decreases in nitric oxide signaling. These findings are congruent with studies in aging men, indicating that the aged rat model may be a valuable tool in analyzing this particular form of ED.

Diabetes

Of all the models of ED, the streptozotocin-induced diabetic rat is one of the most widely employed. This model shows a robust ED when compared with age-matched controls [55]. An important finding is that nitric oxide signaling is decreased in diabetes, and after prolonged diabetes, this decrease of nitric oxide is irreversible, due to the loss of nitric oxide neurons as a result of oxidative stress and advanced glycosylation end products [56–58].

Other studies of diabetes-related ED use the genetically diabetic BB/WOR rat, which is insulin-dependent and ketotic prone form of type 1 diabetes. The BB/WOR rat exhibits severe neuropathy in somatic, sympathetic, and parasympathetic nerves without the compounding angiopathy associated with human diabetes [59]. The copulatory behavioral testing and the study of sexual reflexes confirmed the severe neuropathy associated with ED in the BB/WOR rat. Additionally, these diabetic animals exhibit considerable decreases in penile reflexes, indicative of peripheral neuropathy, but did not show any impairment of the cavernosal nerve-mediated erectile response at 3–5 months of diabetes [60]. Therefore, this animal model may be useful to distinguish between the role of neuropathy and vasculopathy on erectile function in diabetes.

A major research need is the development of robust and satisfactory models of Type 2 diabetes, as this is the most prevalent form of human disease and increasing with the ongoing obesity epidemic.

Hypercholesterolemia

Hypercholesterolemia and subsequent atherosclerosis are well-recognized risk factors for the development of vasculogenic ED [61]. Rarely is hypercholesterolemia-associated ED in men seen in isolation, without other risk factors such as obesity, smoking, age, and diabetes. Rabbits are the most used species in hypercholesterolemia. A high cholesterol/high triglyceride diet, sometimes combined with balloon injury of the aortoiliac arteries, is used to induce atherosclerotic plaques in the arterial supply to the penis. This results in the impairment of endothelium-dependent cavernosal

smooth muscle relaxation and agonist-induced penile erection with papaverine [50, 62, 63]. These defects could not be explained solely by the occlusion of blood flow, but were also accompanied by defects in smooth muscle signaling.

Cavernous Nerve Injury

Due to the high prevalence of ED following pelvic surgery as a result of injury to the neurovascular bundle, there has been a great interest in models of cavernous injury. The goal is to identify the mechanisms leading to the ED (e.g., penile apotosis and fibrosis), as well as identifying methods of preventing these pathological changes or remediating them. The most widely used animal model of cavernous nerve injury (CNI) is the cavernous nerve-injured rat model. Injury can be induced by crush, cut or freezing rat models. Through a lower abdominal midline incision, the posterolateral area of the prostate is exposed on both sides and the major pelvic ganglions and cavernous nerves are identified. The cavernous nerves, unilaterally or bilaterally, are either sharply divided with knives to remove a segment of nerve, cauterized, or frozen using a thermocouple [64–68]. ED-observed postradical prostatectomy is most likely attributed to changes in the endothelium and smooth muscle cells from a loss in neural integrity. The absence of neural input to the penis after CNI in the rat results in cavernosal smooth muscle apoptosis, alterations in the endothelium and smooth muscle function, decrease in neuronal NOS nerve fibers in the penis, pelvic ganglia, and fibrosis. The CNI rat model has led to a more thorough understanding of the pathophysiological sequences involved in the development of postradical prostatectomy ED.

Hypogonadism

Androgens are necessary for the maintenance of the mammalian erectile response. In most animals, androgens are essential in maintaining sexual behavior. However, evidence shows that androgens are also necessary to maintain the erectile apparatus of the penis. Effects of castration on sexual function are evaluated by the observation of copulatory behaviors, penile reflex, and erectile response electrical stimulation of the cavernous nerve. Particularly in the rat model, androgens act centrally to support copulatory behavior and peripherally to maintain constitutive NOS activity and support the veno-occlusive mechanisms. Thus, the erectile response in the rat is androgen dependent [69–74]. Castrated rats have been used as models to study veno-occlusive dysfunction because cavernosal sinusoidal smooth muscle fails to fully relax and blood flow continues during erection in castrated rats, suggesting the failure of veno-occlusion [70, 75]. Despite these reports of the importance of androgens in the erectile response of laboratory animals, the role of androgens in the maintenance of the human erectile response remains controversial. Even in severely hypogonadal men, the erectile response is not always lost. Therefore, the hypogonadal animal model of ED may be best utilized as a model of veno-occlusive ED.

Conclusions

A large number of models exist for the study of male sexual function. Each model has both strengths and limitations. Care must always be taken before extrapolating too quickly from experimental data to a seemingly parallel clinical situation. Practical considerations have led to a great reliance on rodent models. These have the advantage of cost, ease of handling, and a large foundation of biological knowledge. There are rodent models for examining every aspect of penile erection from higher neural control down to molecular events within the erectile tissue. The disadvantage of rodent models is that they do not always accurately reflect human physiology and pathophysiology, although they seem to share many basic mechanisms. Therefore, the validation of any given model must be assessed for a particular application. The utility of these