Experimental Models for the Study of Female and Male Sexual Function

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ABSTRACT

Introduction. Significant progress has been made in the understanding of physiological and pharmacological mechanisms of human sexual functioning through preclinical research in animal models.
Aim. To provide an evidence-based documentation of the experimental models evaluating male and female sexual function for useful clinical translation.
Methods. Consensus discussion over the past 18 months leading to summarized views of seven experts from six countries.
Main Outcome Measure. Report was based on the critical analysis of scientific information available in literature and subcommittee presentations, discussions, and exchanges of ideas and feedback.
Results. Fundamental research in animal models has led to considerable understanding of the physiological mechanisms underlying desire, arousal, genital, and other sexual responses and the design of rational pharmacological treatments for certain sexual dysfunctions in the male and female. Tissue and cellular in vitro systems have provided critical information on the in vivo interactions and modulations in the presence and absence of chemical, biological, vascular, neurologic, endocrine, and genetic inputs. The animal models seem indispensable for elucidating the biophysiological and etiopathological aspects of male and female sexual disorders.
Conclusions. Useful insights into the human experience have been derived from basic research in ways that are far more difficult to obtain in humans, both scientifically and ethically. The animal model with a good predictive value can be used as a successful preclinical tool so long as the functional end points are homologous or analogous. The key issue is whether further evaluations are warranted to extrapolate the results in a clinical setting. **Giuliano F, Pfaus J, Balasubramanian S, Hedlund P, Hisasue S, Marson L, and Wallen K. Experimental models for the study of female and male sexual function. J Sex Med 2010;7:2970–2995.**

Key Words. Animal Models; Male Sexual Function; Female Sexual Function; Behavioral Studies; In Vitro Studies; In Vivo Studies

Introduction

There is much that cannot be studied in humans because of ethical concerns, impracticality, or lack of sufficient technology—preclinical research fills in such a void. Undoubtedly, animal models have aided considerable progress in the past decade in elucidating neuroanatomical and neurochemical mechanisms of erection, ejaculation, and other sexual responses in males and in the design of rational pharmacological treatments for certain sexual dysfunctions in either sex. We have also begun to examine the mechanisms that underlie sexual desire and how sexual stimulation and reward influence attractiveness and mate choice. Nonetheless, appreciation of the importance of animal models is more limited than it needs to be for basic animal

research to be completely extrapolated to a human clinical dysfunction.

Although studies of animal sexuality predate empirical studies of human sexuality, the fact remains that human mating behavior does not really resemble the copulatory behavior in animals. For instance, in rodents which are commonly used to study sexual behavior, gonadal hormones serve two primary functions: to make it physically possible for a male or female to engage in sex, *and* to motivate them to engage in sex [1]. By contrast, in humans and other anthropoid primates, only the latter function of hormones remains, with hormonal influences on the capability to mate, having largely disappeared for evolutionary reasons which are still unclear. Similarly, there is no human equivalent of the lordosis (soliciting gesture), which is under tight hormonal regulation and whose execution is necessary for a male to get an intromission with a female. Although erection is necessary for mating in both rodent and human males, the erectile capacity is no longer under the control of testicular hormones with castrated or hypogonadal men being as responsive to sexual stimuli as males with fully functioning testes. As Miller [2] pointed out more than 75 years ago, humans can mate at any time and under any hormonal condition. Although he believed that this continual capacity to engage in sex was unique to humans, we now know that this is a proclivity that we share with most, if not all, primates and something which distinguishes us from the laboratory rodents, from which we have derived so much of our understanding of the neurochemical and endocrine mechanisms of sexual responding.

At another level of analysis, commonalities between animals and humans have also been shown in studies of sexual pharmacology [3]. For example, the dopamine receptor agonist apomorphine induces erection [4,5], whereas the dopamine antagonist haloperidol reduced sexual arousal and desire [6] both in rats and men. Such results allowed researchers to make a predictive link between the sexual responses of these two species [7–9] and gave rise to an important theoretical implication that certain brain systems had been conserved in evolution to subserve similar or identical functions in this respect. It has led to a new understanding of how animal models can help elucidate mechanisms of sexual behavior in humans—provided that researchers can translate human clinical questions into experimental situations appropriate for the intended animal model.

Requirements of a Good Animal Model

Ideally, animal models must relate in some predictive way to the human condition. At the simplest level of analysis, it is prudent to recognize that all organisms that engage in sexual behavior share common processes. We must be able to respond to hormonal and neurochemical changes that signal our own sexual desire and arousal. This capacity underlies our moment-to-moment level of sexual arousability [10] and defines a large part of the internal state that is commonly referred to as "sex drive." The rest requires a complex mix of instinct, learning and feedback, a neural organization that allows us to interact with external sexual incentives and predict their reactions together with our own responses. We must be able to identify external stimuli that predict where potential sex partners can be found, to seek out, solicit, or court, distinguish external cues and behavioral patterns of willing partners from individuals who are not sexually receptive, and to pursue and execute sexual behavior once such contact has been made. Neural mechanisms exist that allow sexual responding to become habitual or automated with practice and such processes may underlie the ability of sexually experienced animals to be less affected by treatments that disrupt sexual responding in sexually naive animals [11]. Similarly, neural mechanisms allow for the stimulation received during sexual contact to be perceived as rewarding. Such reward alters subsequent behavior, for example, by contributing to the formation of preferences for salient stimuli associated with positive sexual reinforcement [12]. These aspects of sexual responding go well beyond the traditional focus in animal studies on copulation or penile reflexes and make them particularly applicable to human sexual behavior. For all animals, sexual behavior occurs as a sequence or "cascade" of behavioral events. Beach [13] recognized the heuristic value of separating sexual behavior into appetitive and consummatory phases. Essentially, this scheme followed from the work of early ethologists like Craig [14] and experimental psychologists like Woodworth [15], who defined appetitive (or "preparatory") behaviors as those which bring an animal from distal to proximal and into contact with goal objects or incentives. In contrast, consummatory behaviors are performed once an animal is in direct contact with the incentive (i.e., to "consummate" the goal). Consummatory sexual behaviors tend to be species-specific, sexually differentiated, and stereotyped, whereas appetitive behaviors are