Available online at www.sciencedirect.com

SCIENCE DIRECT®

Pharmacology, Biochemistry and Behavior 78 (2004) 379–404

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Review

Preclinical models of sexual desire: conceptual and behavioral analyses

Anders Ågmo*, Anne Lene Turi, Ellinor Ellingsen, Helge Kaspersen

Department of Psychology, University of Tromsø, 9037 Tromsø, Norway

Received 8 February 2004; received in revised form 1 April 2004; accepted 16 April 2004

Abstract

The epidemiology, etiology and proposed treatments for the sexual desire disorders are briefly reviewed before turning to an analysis of preclinical models. We suggest that the concept of sexual desire in the human is equivalent to sexual motivation as employed in the scientific literature. Many animal tests for sexual motivation have been described over the years. Most of them are based on the evaluation of the rate or speed of performing learned operant responses. These are not ideal measures for inferring the intensity of sexual motivation. We present a test for sexual incentive motivation, which has been used in male and female rats. No learning is involved, and the test is rather insensitive to variations in ambulatory activity and it does not employ rate measures. A procedure that recently has attracted much attention, paced-mating behavior in the female, does not seem to be as useful as could be expected. In fact, it does not appear to be superior to tests for sexual receptivity (lordosis). The lack of established, clinically efficient treatments for sexual desire disorders makes it difficult to evaluate if any model has predictive validity. However, the model proposed here may be isomorphic and homologous to the human condition.

Keywords: Hypoactive sexual desire disorder; Hyperactive sexual desire; Paraphilia; Sexual motivation; Sexual behavior; Androgens; Estrogens; SSRI; Bupropion

1. Introduction

Nonhuman animal studies of sexual behavior have been abundant for many years. In fact, the first experimental study we have been able to find was published already in the third quarter of the 18th century (Spallanzani, 1784). During the long history of research on animal sexual behavior, there has been only a handful of serious efforts to explicitly generalize results from nonhuman subjects to the human (see Ågmo, 1999; Ågmo and Ellingsen, 2003, for a more extensive discussion). One reason for this is probably that one very prominent individual in sex behavior research, Frank Beach, considered nonhuman sexual behavior to be heavily dependent on gonadal hormones and hormone-dependent reflexes, while human sexual behavior was less hormone dependent and much less stereotyped (Beach, 1947a,b). Therefore, generalizations from animal to human could not easily be made. Furthermore, animal sex behavior research has been focused exactly on hormone-dependent reflexes, such as lordosis in females and mounting with pelvic thrusting (usually associated with vaginal penetration and eventually ejaculation) in males. Such reflexes are indeed both highly stereotyped and species specific, making generalizations to the human difficult, if not impossible. Thus, by choosing to study the simplest expression of sexual behavior, i.e., copulatory reflexes in laboratory animals, scientists lost the possibility to make meaningful generalizations to the human. This was not considered a problem, though, because much of the work was and is still aimed at elucidating how hormones act on the brain at a cellular, and even molecular, level and in which brain structures they act. One splendid example of this is the clarification of how and where estrogens control the lordosis reflex (summarized in Pfaff, 1999). For this kind of studies, any behavior could have been used, and the lordosis was chosen simply because it is an easily identifiable and quantifiable end point for a behavioral effect of estrogens. Thus, although sexual behavior has been observed and analyzed in many studies, the aim was frequently not to understand that behavior itself (see Ågmo and Ellingsen, 2003, for a discussion).

This situation has changed during the last few years. Growing interest in human sexual disorders and their

* Corresponding author. Tel.: +47-77-64-63-65; fax: +47-77-64-56-10.
E-mail address: andersa@psyk.uit.no (A. Ågmo).

0091-3057/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2004.04.013

treatment has prompted a need for reliable animal models of human sexuality. Attention is also beginning to shift from reflex elements of sexual behavior, like erection, to more complex forms of voluntary behavior, like sexual desire and its manifestations.

In the present review, we will show that the intensity of certain behaviors preceding actual copulation is determined by a mechanism that we conveniently can call sexual motivation. This can be regarded as equivalent to the concept of sexual desire, as it is employed for humans. We will then show that sexual motivation can be quantified. To substantiate this claim, we will present some data from both male and female rats. However, that sexual motivation can be reliably quantified in nonhuman species, and that motivation may be equivalent to desire, is not sufficient for assuming that animal data can be meaningfully generalized to humans. The problem becomes still more complex if we want to test treatments, pharmacological or others, intended for humans in nonhuman animals. Animal models of human disorders need to satisfy a number of criteria (Carlton, 1978; Willner, 1991). To evaluate animal models against these criteria, it is necessary to have some knowledge about the disorder being modeled. This forces us to briefly review the sexual desire disorders in the human before arriving to animal models. First, however, we will try to analyze why animal models of sexual desire have become an important issue only recently.

2. Why a preclinical model of sexual desire disorders, why not and why now?

Usually, if not always, preclinical models refer to one or another human disease. There are, for example, a huge number of preclinical models of pathologies, like anxiety, depression and schizophrenia, just to mention a few. It is evident to most people that models of such disease states are necessary and useful. It has not been and perhaps still is not as evident that there is any need for a model of sexual desire, particularly not for a model of low sexual desire. There are several possible reasons for that. One is that since the time of St. Augustine, sex is only legitimate if the purpose is reproduction. Other purposes transform sexual activity into a sin (Bullough, 1994). When the purpose of sex is reproduction, desire is of slight importance. It is only when sex is performed for recreation that desire starts to become important. But then, it is a sin, and low or even absent sexual desire is a virtue. Thus, for many groups all over the world, including, but not limited to, Judaeo–Christian societies, the notion of hypoactive sexual desire disorder has no sense or it is even ludicrous. Low sexual desire is exactly what should characterize a woman or a man of virtue. To the contrary, hyperactive sexual desire has been pursued and violently punished for centuries (Fout, 1992). Even a need for treatment was recognized, and men convicted of sexual offenses were castrated, sometimes with consent, sometimes without. That castration reduces sexual activity, and, presumably also desire, was already well known among farmers, and the procedure was not considered to be in need of any further preclinical testing.

The notion of low sexual desire as a state of virtue has started to change during the last few years. The main cause is a change in many societies' views on sexuality. It must be pointed out, though, that this attitudinal change is not necessarily associated with any change in actual sexual behavior. Rather, it is so that contemporary sexual norms have come to closer coincide with the behavior that people always have displayed. Already in the late 1940s and early 1950s, Kinsey et al. (1948, 1953) reported that men and women frequently engaged in sexual activity without the purpose of reproduction, and that sexual activities sometimes included orifices other than the vaginal, at that time, both a sin and a criminal offence in the United States and many other countries. Patterns of American sexual behavior did not change much during the following 45 years, as revealed in a survey conducted in the 1990s (Laumann et al., 1994), despite profound changes in attitudes about sex (Robinson and Jedlicka, 1982; Thornton, 1989). A Swedish study from the 1960s (Zetterberg, 1969) reported that there were about 1100 copulations per fertilization among Swedes, showing that sexual intercourse was mainly a recreational activity and only exceptionally associated with reproduction. This, as well as patterns of sexual behavior, had not significantly changed in a subsequent study performed 30 years later (Lewin et al., 1998). Thus, the intensity or frequency of sexual behaviors do not adjust significantly as a result of changing attitudes, and sexual activity appears to have been mainly recreational for a long time.

The separation between sex and reproduction appears to have been complete within the biomedical community around 1960 (see, e.g., Sigusch, 1998). The fact that sexual behavior had become an entity separate from reproduction and, implicitly, that sexual activities could be performed for their intrinsic value made it possible to consider low sexual interest as problematic or even as a disorder instead of as a virtue. This required some time, though, and it was not until 1980 that "inhibited sexual desire" appeared as a diagnostic category in the *Diagnostic and statistical manual of mental disorders, 3rd edition* (American Psychiatric Association, 1980). In the following edition of the manual (American Psychiatric Association, 1987), the label had been changed to "hypoactive sexual desire disorder". In the *International statistical classification of diseases and related health problems, 1989 revision* (ICD-10; World Health Organization, 1992), the name used is "lack or loss of sexual desire".

The inclusion of the diagnostic category of low sexual desire in the main psychiatric manuals was certainly an important event. By itself, however, it was not sufficient to spur interest in preclinical models. The tremendous and unexpected success of drugs for the treatment of erectile deficiencies, sildenafil (Viagra) and its successors, verdanafil (Levitra) and tadalafil (Cialis), has been a decisive factor.

These drugs not only made it evident that there is a need for drugs improving sexual function, but also that many people are willing to pay what they are asked to pay for this kind of drugs. The sildenafil sales of about US$1.7 billion in 2002 and expected verdanafil sales in 2003 of US$1 billion (Harris, 2003) nicely illustrate that. If drugs improving erection can have such a success, it is not impossible that drugs modifying sexual desire may be similarly or even more successful. This kind of reasoning has stimulated a search for drugs that selectively can enhance or block sexual desire. Because preclinical models of human disorders are mainly used for the development and testing of drugs, this is probably the main cause for the recent interest in animal models of sexual desire.

It appears that the advent of sildenafil and, perhaps, orlistat (for the treatment of obesity) and finasteride (for the treatment of pattern baldness), in the late 1990s initiated a debate concerning the role of what is called lifestyle drugs in contemporary medical practice (Klein and Sturm, 2002; Lexchin, 2001; Mitrany, 2001). This discussion has shown that contemporary society is willing to use pharmacological means to enhance satisfaction with life, and that physicians readily prescribe this kind of drugs. It seems as if it has been an attitudinal change so that many people consider that drugs are not only acceptable for alleviating disease but also for enhancing quality of life in absence of organic disease. This attitudinal change is probably part of the sildenafil success, and it has also a salient role in the current interest in finding pharmacological treatments for other sexual disorders, hence, in preclinical models.

3. Epidemiological data on hypoactive sexual desire disorder and some notes on hyperactive sexual desire

Although societal changes have been instrumental for the creation of the diagnostic category of hypoactive sexual desire, such changes alone does not explain the current interest in this disorder and in a potential preclinical model. Studies showing an amazingly high prevalence of the disorder have certainly contributed in a most significant way. An American nationwide survey of 1622 women between 18 and 59 years of age found a prevalence of about 33%, independent of age (Laumann et al., 1994). The same study found prevalence in a sample of 1249 men within the same age range to be around 15%, again, independent of age. A more detailed analysis of the same database revealed a similar pattern of results (Laumann et al., 1999). A study of a representative sample of Danish citizens revealed that 11.2% of the women reported low sexual desire, while the corresponding figure for men was 3.2% (Ventegodt, 1998). Again, there was no relationship between age and the incidence of low sexual desire. In Sweden, 34% of women between 18 and 74 years report low sexual desire as a problem (Fugl-Meyer and Sjögren-Fugl-Meyer, 1999). Only 16% of men did likewise. Interestingly, in the Swedish sample, there was a clear relationship between age and the prevalence of low sexual desire in both sexes. Data from a representative sample of inhabitants of the Valencia-Castellón area in Spain revealed that 37% of the women and 25% of the men complained of low sexual desire (Arnal et al., 1995). Again, there was a marked increase with increasing age in women between 14 and 40 years of age. Thereafter, prevalence remained stable. This shows that menopause has at most a marginal influence, at least in Spain. There was no consistent relationship between prevalence and age in men.

Several studies have determined the incidence of low sexual desire in patients attending primary care centers in several countries. Because the participants in these studies do not constitute representative samples, we prefer to ignore them. Nevertheless, it can be concluded that the prevalence of low sexual desire in women varies from 37% (Spain) to 11.2% (Denmark). In men, the highest incidence is again found in Spain, with 25%, and the lowest in Denmark, with 3.2%. These rather recent data do not differ much from a reanalysis of data from 22 older studies, published over a 50-year period (Nathan, 1986). Many of those studies antecede the creation of the diagnostic category of hypoactive sexual desire. However, estimates of the frequency of the occurrence of psychosexual dysfunctions, as defined by the *DSM-III*, were derived from the original data. The incidence of inhibited sexual desire in men was found to vary between 1% and 15% among these studies. In women, the figures were 1–35%. It appears, then, that low sexual desire was perceived as a problem long before the diagnostic category was established. This reinforces the notion presented above that societal changes in views on sexuality do not affect how sexuality is lived by the individuals conforming the society.

The substantial variations in incidence described in the preceding paragraph probably do not reflect true differences but are rather a result of differences in the way the surveys were conducted, how the questions were formulated, answers classified and other unknown factors. Despite this variability, some unequivocal conclusions can be drawn. One is that low sexual desire is more common in women than in men. However, the difference is not always very large. This means that low sexual desire is a significant problem not only in women but also in men. It is also apparent that low sexual desire is among the most common sexual problems in women (only rivaled by orgasmic disorder). In men, however, it seems that erectile dysfunction and, particularly, premature ejaculation have a higher incidence than low desire (Bortolotti et al., 1997; Kubin et al., 2003; Spector and Carey, 1990).

The fact that hypoactive sexual desire is more common in women than in men requires some comment. First, it must be remembered that the diagnostic criteria demand not only low or absent sexual fantasies and low or absent interest in sexual activities but also marked distress and interpersonal difficulty. Then, it may be observed that there exists a

widely held belief that sexual desire is more intense in men than in women. It even appears that a higher intensity of sexual motivation in men than in women is a most reliable phenomenon, observed in many studies. The lack of contradictory observations may add support to this (Baumeister et al., 2001). If it indeed were the case that men have a higher sexual motivation than women do, then, women would perceive lack of sexual motivation as an interpersonal difficulty more often than men do, at least in stable couples. To the contrary, low motivation in men could bring them down to the level of their partner, thus solving a problem rather than causing one. We believe that this explanation can account for most of the gender difference in the prevalence of hypoactive sexual desire. Another possible explanation is that women simply are more likely to report suffering from this disorder than men are. We have been unable to find any data on this, but it is generally accepted that women report more health problems than men do (Barsky et al., 2001; Ladwig et al., 2000). However, this appears to mainly reflect different incidences of morbidity (Verbrugge, 1985). In fact, differences between men's and women's propensity to report health problems are marginal. This assertion was confirmed in a more recent study (Bogner and Gallo, 2004). Thus, there is not much reason to believe that higher inclination on the part of women to report hypoactive sexual desire can account for any significant proportion of the sex difference in prevalence.

Hyperactive sexual desire does not exist as a disorder category in the *DSM-IV* (American Psychiatric Association, 1995) nor in any other major psychiatric diagnostic manual. Proposals have been made, though, that it should be included in the *DSM-V* and *ICD-11* (Vroege et al., 1998). It has been suggested that the unusually high sexual activity shown by some individuals could be an expression of a hyperactive sexual desire (Kafka, 1997). So far, this condition has only been systematically studied in men. Reports of hyperactive sexual desire in women are limited to case studies and unreliable descriptions of nymphomania (see, e.g., Levine, 1982) and will not be discussed here. Kafka (1997) suggested that men with a total sexual outlet of seven or more orgasms per week during at least 6 months, and who perceived this level of sexual activity as problematic, should be categorized as showing hyperactive sexual desire. Total sexual outlet is understood as all sexual activities leading to orgasm, e.g., vaginal intercourse, oral sex and masturbation. Some data suggest that hyperactive sexual desire is overly common among paraphiliacs and men with paraphilia-related disorders (Kafka and Prenkty, 1992a; Kafka and Hennen, 1999; Kafka, 2000). The incidence of hyperactive sexual desire and of the paraphilias is unknown (Abel and Rouleau, 1990). The number of convictions for certain kinds of sexual offenses could probably provide an estimate of the minimum, but it is presently impossible to obtain a realistic figure of its true prevalence. However, to society, hyperactive sexual desire may be of more concern than hypoactive desire.

4. What is sexual desire disorder and how can it be operationalized?

According to the *DSM-IV* (American Psychiatric Association, 1995), hypoactive sexual desire disorder is characterized by "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician. . .." and "the disturbance causes marked distress and interpersonal difficulty" (p. 510). Some known causes for low sexual desire, like depression or medical or recreational use of certain drugs, must be excluded before the diagnosis of hypoactive sexual desire disorder can be pronounced. There are several subcategories of the disorder, like life-long versus acquired and generalized versus situational.

The expression "desire" is cumbersome when trying to operationalize it, a necessary step in any discussion of preclinical models. According to the Merriam-Webster online dictionary (http://www.m-w.com/cgi-bin/dictionary), the word desire has several meanings: (1) conscious impulse toward something that promises enjoyment or satisfaction in its attainment; (2) sexual urge or appetite; and (3) a usually formal request or petition for some action. The first two may be of particular relevance here. "An impulse towards something that promises enjoyment or satisfaction" can easily be translated to terms used in scientific psychology. A "something" with these properties is exactly what is called a positive incentive in motivation theory (Bindra, 1974, 1976, 1978). Moreover, the "conscious impulse toward" and "urge and appetite" are normally signs of motivation, again, as the term is used in psychology. Combining positive incentive and motivation, we find that desire is equivalent to incentive motivation. If we also take the word "sexual" from the second meaning in Merriam-Webster, we end up with the term sexual incentive motivation as an equivalent to sexual desire. Incentive motivation is normally operationalized as the intensity of approach behaviors, and sexual incentive motivation can therefore be quantified as the intensity of approach towards a sexual stimulus (Ågmo, 1999, 2003). Other aspects of hypoactive sexual desire disorder, like deficient or absent sexual fantasies and marked distress and interpersonal difficulties caused by the disturbance, are probably very difficult, if not impossible, to operationalize in nonhuman subjects. This, however, may be a minor or no problem for the usefulness of a preclinical model because the essential feature of hypoactive sexual desire disorder may be absent or low sexual incentive motivation. The interpersonal difficulties caused by the disturbance may well be a consequence of this and the ensuing low availability for sexual activity. Furthermore, it seems unlikely that absent or deficient sexual fantasies constitute a significant problem if sexual incentive motivation and sexual activity remain intact. In fact, it is likely that reduced or absent sexual incentive motivation is the cause of the lack of sexual

fantasies. If these arguments are correct, then, an animal model of hypoactive sexual desire disorder can do without interpersonal difficulties or absent sexual fantasies.

At difference to our proposal that sexual desire and sexual motivation are equivalent concepts, it has been argued that they need to be separated (Hurlbert et al., 2000). Sexual desire was defined as "a cognitive process to either approach or avoid sexual activity", while sexual motivation is "a behavioral process to either approach or avoid sexual activity" (Hurlbert et al., 2000, p. 326). Most motivation theorists would disagree with this distinction, though, because motivation is not behavior but a factor causing behavior (Bindra, 1974, 1976; Young, 1961). The same factor may also determine cognitive activities. For this reason, the suggested distinction between motivation and desire seems artificial and unfounded in psychological theory.

The conclusion of the arguments exposed above is that the essential feature of hypoactive sexual desire disorder, reduced sexual motivation, can be operationalized for use in studies of nonhuman animals. A fundamental prerequisite for a preclinical model is thereby satisfied.

Hyperactive sexual desire disorder can also be operationalized in a rather simple way. Here, the definition of the disturbance refers to amount of sexual activity per unit time, a total sexual outlet of seven or more per week (Kafka, 1997). This was considered an indicator of hypersexuality because only a small proportion of men attain this level of activity. However, it is not unproblematic to infer the intensity of sexual motivation from the intensity of sexual behavior. We and others (see, e.g., Ågmo, 2002, for a discussion) have presented evidence showing that sexual motivation and copulatory behavior in rats can be partly dissociated. Although no copulation occurs in the absence of motivation, rats may approach a sexual incentive without engaging in any copulatory behavior. Already, Stone et al. (1935) reported that some males would traverse an electrified grid to gain access to a receptive female without ever copulating with her. Nevertheless, there are data showing a correlation between the frequency of sexual fantasies, self-reported sex drive and frequency of masturbation and intercourse in men (Giambra and Martin, 1977; Wilson and Lang, 1981). There seems, therefore, to exist some empirical support for the proposal of Kafka (1997) that hyperactive sexual desire is manifested as unusually high sexual activity. If the same reasoning is applied to nonhuman animals, then, subjects displaying a sexual activity above the normal range could be considered as hypersexual. We will show below that male rats having a high level of sexual incentive motivation also have one aspect of their copulatory behavior facilitated, suggesting that sexual motivation may be inferred from at least one component of copulatory behavior under some experimental circumstances. This does not mean that the intensity of copulatory behavior and sexual motivation are interchangeable concepts, though.

5. Etiology of sexual desire disorders

Little is known about the causes of hypoactive sexual desire disorder. However, one fundamental issue appears to have been tentatively resolved. The issue was whether sexual motivation is intrinsically low or absent or whether it is actively inhibited by some unknown process in individuals suffering from low desire. This was tested in a very elegant study where men, either diagnosed with hypoactive sexual desire disorder or matched healthy controls, were exposed to a series of sexually arousing stimuli (sexual incentives) while regional cerebral blood flow was determined by positron emission tomography (Stoléru et al., 2003). Interestingly, both patients and controls displayed a similar deactivation response in the temporal lobes, thought to be a crucial element of the excitatory process. To the contrary, men with hypoactive sexual desire disorder showed an abnormally maintained activation of the orbitofrontal cortex, known to mediate the inhibitory control of motivated behavior, and low activation of the cingulate and prefrontal regions involved in motor/premotor processes. This latter effect was interpreted as a consequence of deficient motor imagery because of low or no interest in anticipating sexual activities. The conclusion was that hypoactive sexual desire disorder may be a result of active inhibition of an otherwise normal sexual motivation. This very important study needs to be confirmed and extended to women before any definitive conclusion can be reached, but we find the results most suggestive. Moreover, the notion of active inhibition coincides nicely with some behavioral data.

Sexual behavior, particularly orgasm, is regarded as a rewarding event, and it can reinforce learning (discussed in Ågmo, 1999; Ågmo and Ellingsen, 2003; Pfaff and Ågmo, 2002; see also Paredes and Alonso, 1997; Paredes and Vázquez, 1999). This means that the positive affect produced by sexual intercourse leading to orgasm can become associated to environmental stimuli, and these stimuli can thereby become conditioned sexual incentives. Repeated exposure to the same stimuli while experiencing sexual reward will enhance the strength of the conditioning, and the intensity of the experienced reward will probably determine the incentive properties of the conditioned stimuli. To the contrary, absence of the expected reward may have aversive consequences, which may become associated to environmental stimuli. One salient stimulus in a sexual context is the partner. Therefore, it is most likely that the consequences of sex, rewarding or aversive, become associated to the partner and eventually determine her/his incentive properties. In fact, it is well known that the frequency of orgasm is an important determinant of sexual activity and satisfaction (Bentler and Peeler, 1979; Gebhard, 1966; Lief, 1980) and also of motivation (Arafat and Cotten, 1974). For example, the sexual activity most frequently associated with female orgasm, cunnilingus, is also rated as the most satisfying, whereas the activities least associated

with female orgasm, fellatio and anal intercourse, are rated as the least satisfying to women (Hurlbert et al., 1993a,b).

Cues associated with no orgasm could lose their incentive properties or even become aversive, i.e., function as negative incentives. In the latter case, they would not only be unable to activate approach but they would also activate withdrawal. This withdrawal response could be expressed as the active inhibition described in the imaging study mentioned above (Stoléru et al., 2003). This reasoning is not founded upon direct empirical data and should be regarded as hypothetical rather than factual. Moreover, because the absence of orgasm is less frequent in men than in women, it applies mostly, but not entirely, to women. Nevertheless, it must be remembered that hypoactive sexual desire disorder is more common in women than in men. It is also possible that this hypothetical explanation only accounts for some forms of hypoactive sexual desire disorder.

One important study (Trudel et al., 1995) supports a role for a lack of sexual reward in the etiology of hypoactive sexual desire. Couples, in the age range of 20–50, in which at least one had the diagnosis of hypoactive sexual desire, were compared with couples without such a diagnosis. Responses to the Audet and Trudel (1985) sexual behavior inventory revealed that the lifetime sexual behavior repertoire was more limited in couples with low desire, and the pleasure (reward) associated with sexual activities was reduced. In the case of the behavioral repertoire, it is evident that it was more limited in these couples even before the onset of hypoactive sexual desire disorder because the inventory evaluated sexual activities ever experienced and not current activities. Whether the pleasure associated with sexual activities was reduced before the onset of hypoactive sexual desire disorder is impossible to determine from the data presented by Trudel et al. (1995). However, a subsequent study adds some support to the notion that reduced pleasure preceded the onset of the disorder (Trudel et al., 1997). This is exactly what our ''learning'' hypothesis would predict.

More extravagant psychological causes for low sexual interest have been proposed. For example, Kaplan (1995) argues that ''*intrapsychic sexual conflicts and neurotic interactions with the partner*, which presumably have their origins in childhood difficulties, are regarded as the *deeper causes* of psychogenic desire disorders'' (p. 115). This may well be true, but no direct evidence, except clinical experience, is offered in support of this notion. More interestingly, Kaplan (1995) also maintains that hypoactive sexual desire is strongly associated with selectively negative cognitive and perceptual processes with regard to the partner and the avoidance of physical stimulation from the partner. This is, in fact, concordant with our proposal that the partner has acquired aversive properties. It is not sure, though, that Kaplan herself would propose conditioning as the cause.

Others have reported poor marital adjustment as a cause or contributing factor (Trudel et al., 1993), but one study found marital adjustment to be within the normal range in individuals suffering from hypoactive sexual desire disorder (Schiaivi et al., 1992). Moreover, reduced adjustment can easily be explained as a result of low sexual desire on the part of one member of the couple and need not be a causative element. Anxiety has sometimes been suggested to heighten the incidence of low sexual desire in both women (van Minnen and Kampman, 2000) and men (Bozman and Beck, 1991). Still, others have attributed hypoactive sexual desire to comorbidity, such as depression, stress or diabetes (Spector et al., 1993; Trudel, 1991). This is probably not a fruitful approach because the diagnostic criteria exclude individuals with this kind of comorbidity from the diagnosis of hypoactive sexual desire. This also applies to iatrogenic hypoactive sexual desire, frequently observed in depressed patients treated with selective serotonin re-uptake inhibitors. To the contrary, erectile dysfunction has been associated with low sexual desire (Segraves and Segraves, 1991). However, the causal relationship is probably such that low sexual desire leads to problems with erection rather than the opposite. If a man has no interest in engaging in sexual activities, why should he have an erection? It seems that none of the factors mentioned in this paragraph can adequately account for the origin of hypoactive sexual desire as defined in the *DSM-IV*.

There have been some suggestions as to an endocrine basis for hypoactive sexual desire disorder. There is a substantial amount of evidence suggesting that androgens are important for sexual motivation in women (e.g., Davis and Tran, 2001; Sherwin et al., 1985). Consequently, androgens have been quantified in women with hypoactive sexual desire disorder and in appropriate controls. Early studies failed to detect any difference (Schreiner-Engel et al., 1989; Stuart et al., 1987), but a more recent report detected lower free-testosterone concentrations in blood from patients than from controls (Riley and Riley, 2000). At difference to the earlier reports, only patients with life-long hypoactive sexual desire disorder were included. This may, perhaps, account for the different results. Another study reported that a group of normally cycling women with low libido was found to have lower blood testosterone concentrations than did a control group (Guay, 2001), suggesting that androgen deficiency may indeed be related to hypoactive sexual desire.

Other hormones, like estrogens, progestins and prolactin, have now and then been suggested to be involved in hypoactive sexual desire disorder, but there are no consistent results. Furthermore, there is no convincing evidence that any of these hormones is a significant determinant of sexual motivation in women.

Other events have been proposed as causative of low sexual desire, e.g., premenstrual syndrome, oral contraceptives, hysterectomy and oophorectomy, perimenopausal and postmenopausal states, etc. (Warnock, 2002). All these may be important in rare cases, but there is no evidence that they are major etiological factors.

In conclusion, there is no generally accepted hypothesis able to account for the origin of hypoactive sexual desire disorder. The tentative learning hypothesis outlined above

seems to us the most promising, but as mentioned, it is in need of empirical confirmation. Androgen deficiency may also be of importance, but its role has not been firmly established.

In men, the etiology of hypoactive sexual desire is entirely unknown. Low blood concentrations of androgens may be associated with low sexual desire, but most men suffering from hypoactive sexual desire disorder seem to have blood androgen concentrations within the normal range (see LoPiccolo and Stock, 1986, for a discussion). There is no other hypothesis as to etiology that has been subjected to empirical test. This is also the case for hyperactive sexual desire. Nevertheless, the learning hypothesis outlined above could equally well be applied to men both with hypoactive and hyperactive sexual desire, where reduced or absent sexual reward would lead to the former, while enhanced or more frequent reward would lead to the latter. Individuals with unusually high sexual desire are, according to Kafka (1997), individuals who engage in sexual activities with a very high frequency. Thereby, they will have more opportunities to form associations between neutral stimuli and sexual reward than do others. This, in combination with high internal motivation, which may mean enhanced reward value of sexual acts, could explain why at least some of them get sexually attracted to seemingly bizarre stimuli, something typical of the paraphilias.

It is quite possible that both hyperactive and hypoactive sexual desire disorders are the result of a combination of causes, and the contribution of each may vary between one individual and another. Inadequate sexual reward may become decisive only when associated with abnormal androgen concentrations, and the latter may not have any manifest consequence, unless sexual reward is reduced or enhanced, just to take one example. In view of the complexity of the disorders, a multifactorial etiology seems probable, and factors other than learning and hormones need to be considered. Despite this, treatments like hormone therapy or drugs affecting only one of these factors may indirectly affect others, leading to clinical improvement. Current knowledge does not allow for the empirical confirmation of these speculations, though.

6. Treatment of sexual desire disorders

For mysterious reasons, research on the treatment of hypoactive sexual desire disorder has been heavily concentrated on women. It appears that few consider it worth the trouble to search for a treatment for men with this disorder. Therefore, the following discussion will necessarily be focused on women.

There is presently not any established pharmacological treatment for hypoactive sexual desire disorder. A recent review concluded that substitution therapy, basically with androgens, in postmenopausal women is the only well-documented treatment for sexual problems (Everaerd and Laan, 2000). There is, indeed, much evidence suggesting that androgens effectively enhance sexual desire and activity in women with subnormal plasma concentrations of androgens, caused by surgical or natural menopause (Sarrel, 2000; Sherwin and Gelfand, 1987; Sherwin et al., 1985; Shifren et al., 2000). A recent double-blind, placebo-controlled study (Lobo et al., 2003) found that the combination of methyltestosterone (1.25 mg/day) and a most peculiar preparation of estrogens, containing between 75% and 85% of sodium estrone sulfate and between 6% and 15% of sodium equilin sulfate (0.625 mg/day), significantly enhanced sexual desire in a group of postmenopausal women. Only women who experienced reduced sexual desire in association with menopause (natural or surgical) were included. This confirms earlier case studies (Warnock et al., 1999), again, where only women reporting reduced sexual desire in association with menopause were included. These data are not particularly surprising, in view of the large preexisting literature showing that androgens enhance sexual motivation in postmenopausal women. Their importance is probably not overwhelming because the incidence of hypoactive sexual desire disorder among women usually is independent of age. Thus, menopause cannot be a significant etiological factor. In the last two studies mentioned above, menopause was probably the cause of the reduced sexual desire, making their participants highly unusual. It is doubtful whether these studies are of any relevance at all to the vast majority of women with the diagnosis of hypoactive sexual desire disorder.

As mentioned above, however, it is not clear that blood androgen concentrations always are reduced in women with hypoactive sexual desire. Consequently, the use of androgens in premenopausal women diagnosed with this disorder has been rare. In fact, we have been unable to find any study at all where androgens have been administered to cycling women with hypoactive sexual desire disorder. We have to conclude, therefore, that the usefulness of androgens for the treatment of this disorder is impossible to evaluate at present.

Data concerning treatment with psychoactive agents are almost as scarce as those with steroids are. A review in 1996 (Waldinger, 1996) found that no controlled clinical studies of drug therapy for hypoactive sexual desire disorder existed. The situation has only slightly changed thereafter, although some isolated efforts have been made. For example, the noradrenergic α_2 antagonist/5-HT1$_A$ agonist yohimbine was administered to nine women aged between 32 and 49 years diagnosed with hypoactive sexual desire disorder during one menstrual cycle. No improvement was observed (Piletz et al., 1998).

More promising results have been obtained with the mixed noradrenaline/dopamine re-uptake blocker bupropion. A single-blind study revealed that bupropion improved sexual functioning in 29% of a total of 51 women with hypoactive sexual desire disorder after several weeks of treatment (Segraves et al., 2001). This observation should be added to a substantial literature showing that bupropion can alleviate iatrogenic hypoactive sexual desire, induced by specific serotonin re-uptake inhibitors (e.g., Ashton and

Rosen, 1998; Gitlin et al., 2002; Kennedy et al., 2002). There are also data showing that bupropion has prosexual effects, including enhanced sexual desire, in some patients using the drug for the treatment of major depression (Modell et al., 1997). Although these latter studies are of no direct relevance for hypoactive sexual desire disorder, they reinforce the notion that bupropion may be effective in the treatment of it. There is an urgent need of more data on the efficacy of bupropion before any reasonably well-founded conclusion can be reached.

In addition to steroid hormones and psychopharmacological agents, some psychotherapeutic techniques have been employed for the treatment of hypoactive sexual desire disorder (see Heiman, 2002; O'Donahue et al., 1997, for reviews). A four-step intervention program has been used in patients complaining of low sexual desire (LoPiccolo and Friedman, 1988), and it has been reported to produce significant positive effects. However, no adequately controlled study of its efficacy is available at present. A treatment based upon the Masters and Johnson (1970) approach has been claimed to improve sexual desire in over 50% of women completing the program (Hawton et al., 1991), but again, no adequately controlled evaluation of treatment efficacy has been performed.

Another most interesting approach for the treatment of hypoactive sexual desire consists of training women to consistently achieve orgasm during sexual activities, first through directed masturbation (LoPiccolo and Stock, 1986), and later by the coital alignment technique (Eichel et al., 1988). The rationale for this approach is that irregular or absent orgasm may lead to reduced sexual desire. Thus, by training the patients to regularly achieve orgasm, sexual desire should be reestablished. Results from several studies show that orgasm consistency training significantly enhances sexual desire (Hurlbert, 1993; Hurlbert et al., 1993a,b, 1995; Pierce, 2000). It is questionable whether adequate controls were included in these studies, but they constitute probably the most systematic set of data hitherto available on psychological treatments of hypoactive sexual desire disorder. In fact, the orgasm consistency training program is the only treatment included in the American Psychological Association's list of probably efficacious treatments (Chambless et al., 1998). No therapy for hypoactive sexual desire disorder is considered as empirically validated.

It may be interesting to note that the encouraging, albeit preliminary, results of orgasm consistency training reinforces the hypothesis presented in the Etiology section that hypoactive sexual desire may be a result of repeated lack of reward in association with sexual activity. Incentive stimuli associated with sexual activity lose, thereby, their positive incentive properties, hence, their capacity to activate sexual desire. Because orgasm gives rise to a rewarding state, as mentioned in the appropriate context, this state should become associated to the behaviors immediately preceding it and the concurrent stimuli, thereby turning them into conditioned positive incentives. The more consistent orgasm is, the faster the associations between the rewarding state and the concurrent stimuli will develop.

Very little is known about treatment of male hypoactive sexual desire. In the rare cases where hypogonadism is the cause, treatment with androgens may be efficient (Bancroft, 1984; Burris et al., 1992). However, such cases should not receive the diagnosis of hypoactive sexual desire disorder, according to the *DSM-IV*, because the cause is a general medical condition. Therefore, it must be concluded that androgens are ineffective in this disorder when correctly diagnosed. A complex cognitive–behavioral treatment have been reported to have positive effects, but no controlled study has been performed (LoPiccolo, 1985; Schover and LoPiccolo, 1982). A treatment based on behavioral sex therapy has been reported to have a success rate of about 65% and to be equally effective in male and female hypoactive sexual desire (Sarwer and Durlak, 1997). Control groups were missing. An essential element in the program was daily exercises of sensate focus, progressing from facial touching to mutual masturbation, and finally to intercourse. Another program, a mixture of communication exercises, sexual fantasy exercises and sensate focus training (McCabe, 1992), has also been reported to have a substantial success rate (McCabe, 2001). Again, adequate controls were missing. It may be noted that sensate focus training (Masters and Johnson, 1970) was employed in all treatment programs. This training is, particularly in the later phases, inevitably associated with sexual reward. It provides, then, many occasions for forming associations between the sexual reward and the partner, thereby enhancing his/her sexual incentive properties. In essence, sensate focus and orgasm consistency training may work in similar ways with regard to reward learning.

Hyperactive sexual desire has usually been treated with drugs. One approach has consisted of turning one of the most common side effects of specific serotonin re-uptake inhibitor antidepressants, reduced sexual functioning, into a therapeutic effect. Both fluoxetine, sertraline and fluvoxamine have bee reported to be effective in paraphilia and paraphilia-related disorder (Greenberg and Bradford, 1997; Greenberg et al., 1996; Kafka and Prenkty, 1992b). Another approach has employed drugs either blocking androgen receptors or reducing the release of pituitary gonadotrophins. The androgen antagonist cyproterone has been reported to reduce sexual behavior, sexual fantasies and arousal (Bradford and Pawlaka, 1993). Medroxyprogesterone, a progestagen reducing pituitary release of gonadotrophins and, thereby, blood concentrations of androgens, has also been successfully used (Meyer et al., 1992). This drug, as well as cyproterone, are no longer used in Europe. They have been replaced with LH-RH agonists, which deplete pituitary gonadotrophin reserves and eventually lead to important reductions in blood androgen concentrations. Two of these agonists, leuprolide and triptorelin has been extensively used and are reported to significantly reduce sexual desire (see Briken et al., 2003, for a recent review). That much reduced circulating levels of androgens diminish sexual behavior and

desire is concordant with a large, older literature showing that castration leads to exactly this (see, e.g., Bremer, 1958; Wantoch, 1935). Whether androgen concentrations are reduced by surgical or pharmacological means should, in fact, not alter the end result.

The main problem with all the studies mentioned is that most of them are limited to individuals convicted for sexual offences and most of them lack adequate controls. Data from nonconvicts are scarce. Nevertheless, with regard to the serotonin re-uptake inhibitors, there is a large amount of data showing that they reduce sexual desire in some patients being treated for depression. Whether they have this effect in healthy individuals is unclear.

There have been some efforts to treat hypersexuality with different kinds of psychotherapy (see Abel and Osborn, 1996; LoPiccolo, 1992; Vogelgesang, 1999). Among the many approaches employed, one may be of interest here: aversive conditioning consisting of pairing sexual responses to inappropriate stimuli with noxious odors (Laws and Osborn, 1983; Maletzky, 1980) or electric shock (Rice et al., 1991). Such procedures have been reported to be effective in reducing the response to the stimuli employed (Quinsey and Marshall, 1983), but no adequately controlled studies are available (Quinsey et al., 1993). Because aversive conditioning is judged to be inhumane and is rarely, if ever, used today, it will probably never be established whether it really is an effective treatment or not.

7. Criteria for a good preclinical model of sexual desire

In a discussion of purported animal models of homosexuality, Beach (1979) pointed out that a meaningful model should not be based on formal similarities of behavior, but upon its causal mechanisms and functional outcomes. Furthermore, the validity of interspecific generalizations cannot exceed the reliability of intraspecific analysis. These basic principles should also apply to animal models of sexual desire. However, and insofar as the purpose of an animal model of sexual desire is to predict the effects of pharmacological agents in the human, simple correlational criteria are probably sufficient just as they are in other animal models (see, e.g., Treit, 1985). One correlational criterion is that the animal model should be sensitive to standard compounds known to be therapeutically effective. Moreover, the relative potency of known drugs should be similar in the human and in the animal model. It should also be selective so that drugs ineffective in the human also should be ineffective in the animal model. This set of criteria is highly useful when animal models of anxiety, schizophrenia, depression, etc., where a large amount of clinically effective drugs exists, are validated. However, in the case of hypoactive sexual desire disorder, there does not exist any drug with proven clinical effect. As mentioned, some preliminary data suggest that bupropion may be clinically active in women, but this is far from established. Even if it would be so, it is difficult to analyze correlations with only one point available. Relative potency and selectivity would be extremely difficult to demonstrate. To do that, a number of drugs with proven clinical efficacy would have to be ranked according to the dose needed for clinical effect. Then, the same drugs would have to be ranked according to the dose needed for effect in the animal model. Ideally, the rankings should coincide. To determine selectivity, it would be necessary that drugs active in the clinic would be so also in the animal model, while drugs having no clinical effect should have no effect in the model. This means that correlational criteria can be used only when a number of clinically effective drug treatments exist, which is not the case for sexual desire disorders.

One partial solution to the problem of paucity of pharmacological treatments could be to add androgen agonists and antagonists to the repertoire of clinically effective drugs. As discussed in the Treatment section above, however, the evidence for an effect of androgens in hypoactive sexual desire is limited to postmenopausal women, and even there, the data are not overwhelming. In men with hyperactive sexual desire, reduction of blood concentrations of androgens, or the blockade of androgen receptors, seem to be effective. These data could perhaps be used for testing a correlational criterion in an animal model of male hyperactive desire. Nevertheless, the inevitable conclusion is that correlational criteria are not easily applied to animal models of sexual desire. In most other preclinical models, e.g., models for the evaluation of anxiolytics, antispychotics or antidepressants, the correlational criteria are frequently the only ones employed and even the only ones possible to employ. This fact puts models of sexual desire in a different category.

The adequacy of a preclinical model may also be judged by isomorphism, the similarity of behaviors displayed in the human and in the animal model. With similarity, it is not necessarily meant that the exact motor patterns displayed are identical or even equivalent. Rather, it refers to the result or the "purpose" of the behaviors. In the case of sexual desire or sexual motivation, the result or purpose would be a successful approach to a potential mate and establishment of contact, eventually leading to copulation. Procedures for evaluating the intensity of approach behaviors and for the transition from approach to copulation are readily available in nonhuman animals. Thus, it can be maintained that at least some preclinical models of sexual desire are isomorphic.

An ideal preclinical model should be homologous to the state it models; that is, the underlying causes or behavioral processes should be similar in the human and in the animal model. There is much reason to believe that the basic neural and behavioral mechanisms controlling sexual desire or motivation are similar in rodents and in humans (see Ågmo and Ellingsen, 2003 and Pfaff, 1999, for a discussion). In this way, rodent models can be considered homologous. However, the category "hypoactive sexual desire" is not easily defined in nonhuman animals. The existence of rare or absent sexual fantasies cannot be determined, and interpersonal problems because of low sexual desire are difficult to

define and describe. Nevertheless, low sexual motivation can easily be produced in nonhuman animals through some experimental procedures (see below). There is also a substantial proportion of rats displaying life-long hypoactive sexual desire, at least in the sense that they display no copulatory behavior under standard testing conditions (Whalen, 1964; Whalen et al., 1961). Noncopulating male rats do not show any preference for sexually receptive females or the odor thereof. This has been interpreted as a consequence of reduced sexual motivation (Portillo and Paredes, 2003). Furthermore, as will be discussed below, there are procedures for the conditioning of low sexual motivation in rats. Such procedures have been intentionally employed in hypersexual men, and unintentional conditioning may contribute to low sexual desire in both women and men. The similar consequences of learning in humans and other animals could constitute an indication of homology. However, because the etiology of hypoactive and hyperactive sexual desire disorders is not adequately known, it is not possible to assure that rodents with altered sexual motivation are homologous to humans suffering from a similar condition. At the same time, it is impossible to assure that they are not. Thus, at present, it is not known whether animal models of sexual desire are homologous. However, below, we will present some data suggesting that they are.

There is no way to determine whether preclinical models of sexual desire have predictive validity through the use of correlational criteria. To the contrary, such models are probably isomorphic and, perhaps, even homologous. This makes it likely that they possess predictive validity for drug effects. In addition, these models might be helpful for the further analysis of the potential causes of hypoactive and hyperactive sexual desire disorders.

8. Overview of procedures for studying sexual motivation in nonhuman animals

In Section 3, we suggested that sexual desire is equivalent to what is called sexual motivation in animals. Therefore, because we will now concentrate on rodents, the term motivation will be consistently employed, except when directly referring to the human. The theoretical bases for experimental procedures for the study of sexual motivation, as well as advantages and disadvantages with different approaches, have been extensively discussed elsewhere (Ågmo, 1999; Pfaff and Ågmo, 2002). Only a summary will be presented here.

Ex copula sexual reflexes in the male have been much employed in studies of rodent sexual behavior. One such reflex is spontaneous seminal emission, frequently associated with spontaneous erection. The latter event can be studied by itself. Spontaneous erection/seminal emission occurs with low frequency and is therefore a rather impractical behavior to observe. The frequency of erection can be enhanced by exposing the male to an inaccessible female or to the odor of a female. Such spontaneous erections are then called noncontact erections (Sachs, 1997); we prefer the term female-enhanced spontaneous erection. It has been suggested that the frequency of this kind of erections is an indicator of sexual arousal (Sachs, 2000). This may be the case, but they are certainly not an indicator of sexual motivation. Males with lesions in the preoptic area, which dramatically reduce copulatory behavior, show normal female-enhanced spontaneous erections (Liu et al., 1997).

Males with preoptic lesions do not only display reduced sexual behavior, but also impaired sexual motivation (see Paredes, 2003, for a review). Such males show no preference for a receptive female over a nonreceptive one (Edwards and Einhorn, 1986; Paredes and Baum, 1995; Paredes et al., 1998), and their sociosexual behavior towards a receptive female is altered (Paredes et al., 1993). Moreover, inactivation of the medial preoptic area with lidocain reduces sexual incentive motivation in addition to eliminating copulatory behavior (Hurtazo et al., 2003). Finally, an androgen receptor antagonist administered to the posterior preoptic area blocks the restoration of sexual partner preference by systemic testosterone in castrated male rats (McGinnis et al., 2002). It may be observed, though, that while unconditioned sexual motivation disappears after preoptic lesion, some data suggest that conditioned sexual motivation may persist. Rats subjected to a complex second-order conditioning procedure continue to press a lever for access to a receptive female even after preoptic lesion (Everitt, 1990; Everitt and Stacey, 1987). Because we here limit our discussion to unconditioned sexual motivation, these observations are not pertinent.

The fact that preoptic lesions reduce sexual motivation, while leaving female-enhanced spontaneous erections unaffected, suggests that they are not expressions of sexual motivation. This notion is reinforced by data showing that lesions in the medial amygdala, which almost eliminate female-enhanced spontaneous erections, do not affect copulatory behavior and do not reduce preference for receptive females over anestrous ones (Kondo and Sachs, 2002). Insofar as motivation refers to the urge to seek sexual contact and engage in sexual activity, these males did not show impaired motivation. In sum, it appears that female enhanced spontaneous erections are not indicators of sexual motivation. They may, however, be sensitive to sexual arousal as understood in the human literature and as suggested by Sachs (2000). In the human, sexual arousal refers to enhanced genital blood flow, manifest as erection in men and vaginal engorgement and lubrication in women. This kind of arousal is quite different from motivation as understood in the context of nonhuman animal studies.

Penile reflexes may also be studied in tests where the male is restrained in a supine position with retracted penile sheath. This allows for a more detailed analysis of penile movements. In such tests, erection (engorgement of the penile body) may be associated with anteroflexion of the penis, a movement dependent on the ischiocavernosus muscles and necessary for intromission. It may also be associated with

intense engorgement of the glans penis, an event dependent on contraction of the bulbospongiosus muscles, and necessary for the deposition of the sperm plug at ejaculation (Sachs, 1982). The ease of activation of these muscles can reasonably be regarded as dependent on motivation. Unfortunately, experimental manipulations may have opposing effects on these penile reflexes and on copulatory behavior (e.g., Smith et al., 1987), suggesting that the mechanisms controlling these reflexes are not identical to those controlling copulatory behavior. Furthermore, activity in the ischiocavernosus and bulbospongiosus muscles appears to be of little importance for copulatory behavior in men. This means that ex copula penile reflexes are not isomorphic. These facts make them unsuitable as an animal model of male sexual motivation. Peripheral reflexes in the female rodent, like vaginal blood flow, have neither been employed nor suggested as measures of sexual motivation.

Copulatory behaviors, lordosis in the female and mount with pelvic thrusting with or without intromission/ejaculation in the male have sometimes been used as indices of motivation. Both lordosis and mount with pelvic thrusting are tactile reflexes (Contreras and Ågmo, 1993; Pfaff et al., 1973). Conceptually, it is entirely legitimate to employ their ease of activation as a measure of motivation because the internal processes determining this must be considered as motivational. Although lordosis and mount (with or without intromission/ejaculation) are consummatory behaviors and belong to the category of fixed action patterns, or reflexes, their display is a result of an interaction between an external stimulus and an internal state. This internal state is usually called motivation (Lorenz, 1950; Pfaff, 1982a,b). In the female rat, copulation is frequently associated with proceptive behaviors, hop darting and ear wiggling (in fact, rapid dorsoventral movements of the head). These behaviors are often considered appetitive behaviors, despite that they are displayed during copulation, as well as shortly before. While lordosis is a purely tactile reflex, proceptive behaviors appear to be both tactile and olfactory reflexes. They are activated by physical contact with a male, and a gonadally intact male is about twice as effective as a castrated one (Vreeburg and Ooms, 1985). This latter observation suggests a role for olfactory stimuli in addition to the tactile stimulation equally provided by the intact and the castrated male. Although proceptive behaviors are less well studied than the lordosis is, they can also be considered as fixed action patterns or reflexes. As such, their intensity and/or ease of activation are controlled by motivation in the same way as lordosis is. Nevertheless, in an extensive review of proceptive behaviors, Beach (1976) avoided to attribute any particular motivational significance to them.

The copulatory reflexes are highly stereotyped and species specific. In most nonhuman animals, among these, rodents, copulation is essentially limited to repeated activation of such stereotyped reflexes. On the contrary, copulation in the human is only partially determined by reflex movements. Obviously, the autonomous reflex of erection is necessary for vaginal intercourse, and vaginal lubrication is helpful. Nevertheless, actual copulatory behavior can be highly variable. Moreover, sexual activities other than vaginal intercourse are not necessarily dependent on erection or vaginal lubrication. It seems, therefore, that copulatory behavior is not isomorphic in men and in rats. This means that the study of copulation, i.e., sexual reflexes in sequence, is not ideally suited for predictions from animals to humans. However, this rather negative view on copulation needs to be interpreted with some caution. There is at least one case where the inhibitory actions of drugs on lordosis in female rats and on male rat copulatory behavior coincide with human data. Agents enhancing serotoninergic neurotransmission was shown to inhibit lordosis in females (Meyerson, 1964a,b) and to reduce mounting in males (Malmnäs, 1973) many years before the adverse sexual side effects of specific serotonin re-uptake inhibitor antidepressants were described in the human (Rosen et al., 1999; Segraves, 1998). Moreover, the capacity of some serotonergic agonists to prolong ejaculation latency in rats (e.g., Ahlenius et al., 1980) coincides with their usefulness in treating premature ejaculation in men (Atmaca et al., 2002; McMahon and Touma, 1999; Waldinger et al., 2001).

Instead of studying penile reflexes or copulatory behavior, events preceding actual copulation may be the subject of study. Copulatory behavior can only take place when two (or more) individuals are in close proximity. In standard tests for copulatory behavior, the experimenter assures this proximity by confining individuals in a small area. However, in a natural setting, the first requirement for sexual interaction is the localization of and approach to a potential mate. Approach behaviors are *not* stereotyped but highly variable and determined by the momentaneous context. Thus, approach does not consist of a specific motor pattern but of arbitrary movements leading to a reduction of the distance to the potential mate. Interestingly, a stimulus able to activate approach behaviors is called a positive incentive, and the intensity of approach is a measure of the intensity of incentive motivation. We have argued extensively that sexual motivation is a prototypical case of incentive motivation (Ågmo, 1999, 2003; Pfaff and Ågmo, 2002). Moreover, because approach behaviors are arbitrary and, consequently, most variable, but have a fix consequence, the attainment of closeness to the mate in animals and humans, they can be considered to be isomorphic. Studies of the intensity of approach to a mate are, therefore, ideally suited for the evaluation of sexual motivation.

Many tests for sexual incentive motivation employ learned operant responses, like running in a runway or bar pressing for access to a mate (e.g., López et al., 1999; Matthews et al., 1997). Such responses can be used to infer motivation only when learning is asymptotic. If not, the effect of an experimental manipulation may be on learning just as much as on motivation. Even at asymptotic learning, though, effects of experimental variables on motivation can easily be confounded with effects on memory. Does the male rat run slower in the runway because its sexual motivation

was reduced or because it had forgotten that there was a receptive female in the goal box? The answer to that question might perhaps be obtained through some control experiments, but it can also be very difficult to eliminate the memory explanation. This ambiguity can be circumvented by the use of an unlearned response.

Another, and perhaps even more serious, problem with operant procedures is that motivation is inferred from the rate or speed of responding. As soon as we introduce experimental manipulations, particularly drug treatments, we are likely to affect motor functions, especially if large doses are employed. The result of this is that motor effects are confounded with effects on motivation. This confound is still worse in procedures where conditioned or unconditioned locomotor activities are taken as indicators of sexual motivation (Mendelson and Pfaus, 1989; Pfaus et al., 1999). To avoid this confound, it is essential to have an independent measure of motor function. This is not easy in a runway where the speed of running is used as indicator of motivation, or in a standard Skinner box, where the rate of lever pressing is the dependent variable. Procedures using measures of motivation not based on speed or rate of response seem more adequate.

The preceding discussion should have made it clear that a test for sexual incentive motivation where the requirement for motor activity is minimized would be ideally suited as a preclinical model of sexual desire.

9. A test for sexual incentive motivation in rats as a model

A large circular open-field containing an intact and a castrated male confined to separate wire mesh enclosures fixed to the wall, was employed many years ago for testing sexual motivation in female rats (Meyerson and Lindström, 1973). The same procedure was later also used in males (Hetta and Meyerson, 1978). A crucial difference from earlier procedures was that no sexual interaction was possible. Thus, this test evaluated sexual incentive motivation in the absence of copulatory behavior. These early studies showed that females treated with estradiol benzoate + progesterone approached the active male more than the castrated male, and that androgens, either from the testicles or from an exogenous source in the case of castrated animals, were necessary for a male to approach a receptive female more than a castrated male does. In all these studies, sexually experienced subjects were used, although it later was reported that animals without sexual experience responded in the same way (Meyerson et al., 1979). A modification of this procedure was later employed in some studies (Vega-Matuszczyk and Larsson, 1991, 1993, 1994; Vega-Matuszczyk et al., 1994). Again, gonadal hormones were found to be necessary for approach to a sexually active animal over that to a sexually nonactive animal.

During the last few years, we have undertaken a series of studies with the purpose of unequivocally showing that this kind of procedure adequately quantifies sexual motivation, both in male and female rats. Some of the data have been published elsewhere (Ågmo, 2003) and will not be repeated here. In the following, we will limit our presentation to cover two fundamental issues: Does this procedure really measure sexual motivation and can it be employed as a model of human sexual desire?

The measure of sexual incentive motivation obtained in the procedure is the time spent in an area adjacent to an inaccessible sexual incentive compared with the time spent in an area adjacent to a social, nonsexual incentive (Fig. 1). Thus, rather than quantifying the speed or rate of response, the procedure employs permanence in a particular area as an index of motivation. The motor capacities required for remaining in a certain place on a flat surface are not exacting, but the subject needs to display some level of ambulatory activity to reach the area and explore the alternative incentive area. Therefore, variables like distance moved during the test, speed of movement and immobility time are always recorded. In case the experimental treatment has effects on ambulatory activity, caution is needed when interpreting the results. Alternatively, indices of ambulatory activity can be used as covariates in the analyses, thereby reducing or eliminating the confound caused by effects on motor functions. The fact that ambulatory activity can be assessed simultaneously with, but independently from, parameters of motivation is an important advantage of the procedure.

If the experimental subject is a male rat, then, the sexual incentive is a female (ovariectomized, treated with estradiol benzoate, 25 μg, + progesterone, 1 mg, at − 48 and − 6 h, respectively, test time being 0), and when the subject is a female, the sexual incentive is a sexually active, intact male

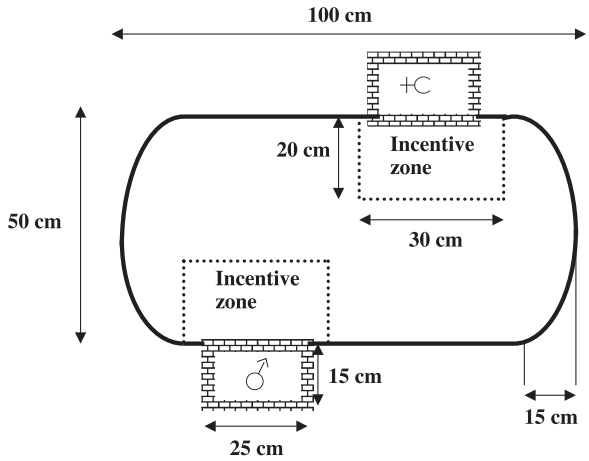

Fig. 1. Drawing of the sexual incentive motivation test arena. The incentive animal cages are removable and can easily be exchanged within experimental sessions. Outside these cages, a virtual zone is defined. The arena is surrounded by a 45-cm-high wall, and the incentive animal cages are 25 cm high. These cages have the front made of wire mesh (mesh size 12 × 12 mm), and they are attached to openings in the arena wall. Reproduced from Ågmo (2003), where further details can be found. Copyright 2003 by the American Psychological Association. Reprinted with permission.

rat. A receptive female, as well as an intact male, readily initiates copulation when given the opportunity to do so. They are, then, sexual incentives. The social incentive is another male when a male is the subject, and a castrated male when a female is the subject. A male rat normally does not try to copulate with other males, and a castrated male will display no sexual behavior with a receptive female. These animals are social, nonsexual incentives. The intensity of sexual motivation can be expressed as a preference score, time spent in vicinity of the sexual incentive/(time with this incentive + time spent in the vicinity of the social incentive) or as the difference in time spent in the vicinity of a sexual versus a nonsexual incentive. It can be maintained that the sexual incentive is approached for two reasons: search for a sexual partner and/or a social encounter. The social incentive is approached for one reason: a social encounter. The difference between the sexual and the social incentive should therefore represent the intensity of sexual motivation unconfounded with social motivation. This reasoning needs, and has obtained, experimental support.

Another animal can have sexual incentive properties only under the condition that the experimental animal indeed is seeking sexual contact. In the procedure described here, sexual contact is potential rather than factual because of the wire mesh separating the experimental subject from the incentive. Even the potential sexual contact can be excluded by eliminating gonadal hormones from the subjects. It is well known that ovariectomized females will display no sexual behavior unless treated with gonadal hormones, and a castrated male will likewise not show any copulatory behavior, provided that some time has passed after castration. On the contrary, the social incentive properties of the social incentive should not change when gonadal hormones are absent. Consequently, a castrated male or a spayed female should spend about the same time with the sexual and the social incentives.

As can be seen in Fig. 2A and B, the time that the male rats spent in the vicinity of a receptive female got reduced after castration, while the time spent in the vicinity of another male was not modified. Furthermore, the interest in the receptive female regains precastrational level after treatment with testosterone propionate. This means that the experimental subject's response to the sexual incentive is modified exactly as predicted, and the response to the social incentive does not change, also as predicted. Fig. 2C shows that the difference between the social and the sexual incentives, i.e., the intensity of sexual incentive motivation, disappears after castration and reappears after treatment with testosterone propionate but not after oil treatment. Another way of quantifying sexual incentive motivation, the prefer-

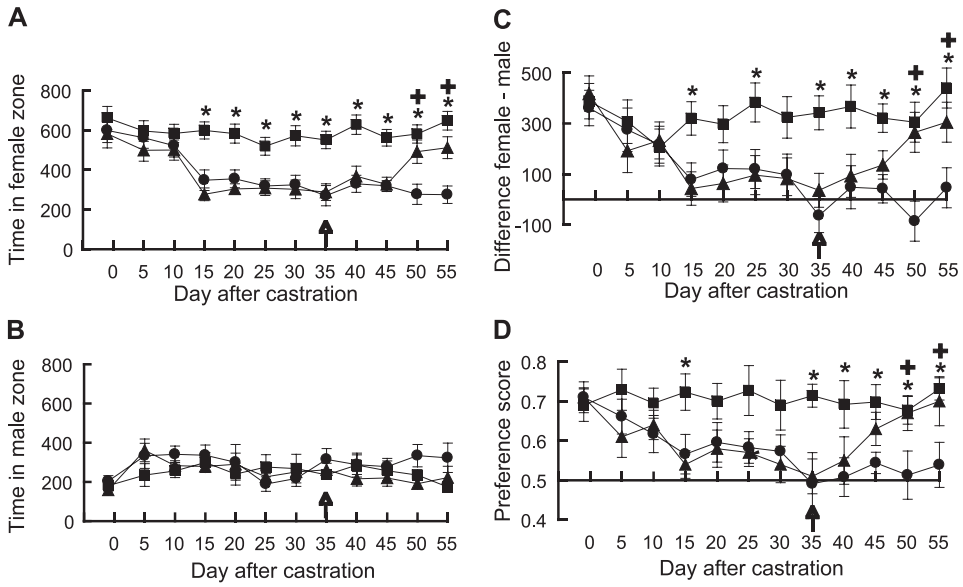

Fig. 2. Time spent in the receptive female (A) and in the male (B) incentive zones, as well as the difference between time in the female zone and time in the male zone (C) and the preference score (D). The difference between zones should represent the intensity of sexual incentive motivation when social motivation has been subtracted. The preference score represents the proportion of the total time spent in the incentive zones that was spent in the sexual incentive zone. A score of 0.5 indicates that the experimental subjects spent equal times with the sexual and the social incentives. There were 12 animals per group. Data are mean ± S.E.M. Time is given in seconds. Tests lasted 20 min. ■: Intact; ●: castrated on Day 0 and given an injection of oil, 1 ml/kg, twice a week from Day 35 and on; ▲: castrated on Day 0 and given an injection of testosterone propionate, 2 mg/kg, twice a week from day 35 and on. Statistics: (A) Main effect of group (intact, castrated + oil, castrated + TP): $F(2,33) = 14.19$, $P < .001$; main effect of test day: $F(11,363) = 4.46$, $P < .001$; interaction Group × Test Day: $F(22,363) = 3.05$, $P < .001$. Because of the significant interaction, tests for simple effects of group at each test day were performed. When significant, Tukey's HSD test was used to determine group differences. The significances illustrated in the figure are based on this latter test. (B) Main effect of group: $F(2,33) = 2.71$, NS; main effect of test day: $F(11,363) = 2.06$, $P < .05$; interaction Group × Test Day: $F(22,363) = 1.21$, NS. (C) Main effect of group: $F(2,33) = 11.73$, $P < .001$; main effect of test day: $F(11,363) = 3.47$, $P < .001$; interaction Group × Test Day: $F(22,363) = 1.84$, $P < .05$. Tests for simple effects were performed as in Panel A. * Intact group compared with the castrated + oil group, $P < .05$; $^{+}$ castrated + testosterone propionate group compared with the castrated + oil group, $P < .05$. Modified from Ågmo (2003). Copyright 2003 by the American Psychological Association. Adapted with permission.

ence score, is illustrated in Fig. 2D. Again, preference score approaches 0.5 (no preference) after castration and starts to increase above that level soon after testosterone replacement. These data add support to the notion that it is sexual incentive motivation that is measured in the procedure, at least in males.

It might be argued that the larger time spent with the receptive female in intact or testosterone-treated subjects is a consequence of some aversive properties of the social incentive and that these aversive properties are dependent on the hormonal state of the experimental subject. This possibility was tested in an experiment where the sexual incentive was absent. Thus, the subjects could choose between an empty cage and an intact male, the habitual social incentive. In another experiment, they could choose between an empty cage and a cage containing an ovariectomized female, another social incentive. In Fig. 3A, it can be seen that the subjects spent far more time in the vicinity of the other male than in the vicinity of the empty cage. This shows that the other male, by no means, is aversive. Similar results were obtained with the ovariectomized female (Fig. 3B). These observations confirm a series of studies demonstrating that laboratory rats are gregarious and actively seek social contact with other rats, even of the same sex (Eckman et al., 1969; Latané, 1969; Latané and Glass, 1968; Latané et al., 1972, 1973). If the subject is allowed to choose between an empty cage and a receptive female, it turns out that he strongly prefers the female. When comparing the difference between an empty cage and another male as incentives with the difference between an empty cage and a receptive female, it turns out that the latter is significantly larger (see Fig. 3A). Data from the experiment where an ovariectomized female was used instead of a male show similar results (Fig. 3B). When making these latter comparisons, we have compared the incentive properties of another male or an ovariectomized female, social incentives, with that of a receptive female, both of which are social *and* sexual incentives. The difference between the incentives constitutes the intensity of sexual motivation, as already pointed out. Instead of making multiple comparisons between different incentives and empty cages, it is much easier to introduce both social and sexual incentives at the same time and compare them directly. The end result should be the same, and that is the standard procedure we use.

To further validate the procedure we performed a motivation test in some males having had free access to receptive females for 4 h. It was reasoned that extensive sexual activity immediately preceding the test should reduce sexual motivation. In fact, 4-h access to females is known to produce sexual exhaustion (e.g., Rodríguez-Manzo and Fernández-Guasti, 1994), which is a state where the male will not copulate when given the opportunity to do so. As expected, sexual motivation was much reduced (Fig. 4).

Also in females, the preference for the active over the castrated male is hormone dependent. Ovariectomized females given injections of oil spent about the same time

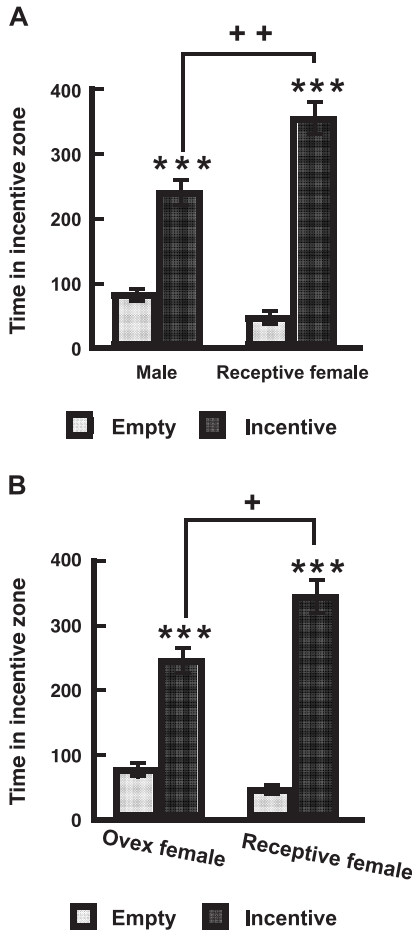

Fig. 3. (A) Time (seconds) that male rats spent in the incentive zones in an experiment where either one incentive cage was empty and the other contained another male (Male) or one cage was empty and the other one contained a sexually receptive female (Receptive female). (B) Similar data from an experiment where the choices were either between an empty cage and an ovariectomized, nonreceptive female (Ovex female) or between an empty cage and a receptive female (Receptive female). Data are mean ± S.E.M., $n = 8$ in both groups. Test duration was 10 min. Statistics: (A) Main effect of incentive (empty cage vs. male or receptive female): $F(1,7) = 95.58$, $P < .001$; main effect of choice condition (empty vs. male; empty vs. receptive female): $F(1,7) = 44.91$; interaction between incentive and choice: $F(1,7) = 22.02$, $P < .01$. Interaction means were compared using Tukey's HSD procedure, with $k = 4$. It is the results from this test that are illustrated. (B) Main effect of incentive (empty cage vs. ovariectomized or receptive female): $F(1,7) = 115.97$, $P < .001$; main effect of choice condition: $F(1,7) = 9.03$, $P < .05$; interaction between incentive and choice: $F(1,7) = 10.99$, $P < .05$. The Tukey HSD test for used for comparisons of interaction means as in Panel A. *** Different from the empty cage, $P < .001$; $^{++}$ different from the time spent in the male incentive zone in the test with empty cage—another male, $P < .01$; $^{+}$ different from the time spent in the ovariectomized female incentive zone in the test with empty cage—ovariectomized female, $P < .05$.

in the vicinity of the castrated and intact males, whereas females treated with estradiol benzoate + progesterone showed a clear preference for the active male (Fig. 5). This is also the case when progesterone is omitted. The time spent in the vicinity of the castrated male did not change according to hormone treatment. The conclusion drawn from this

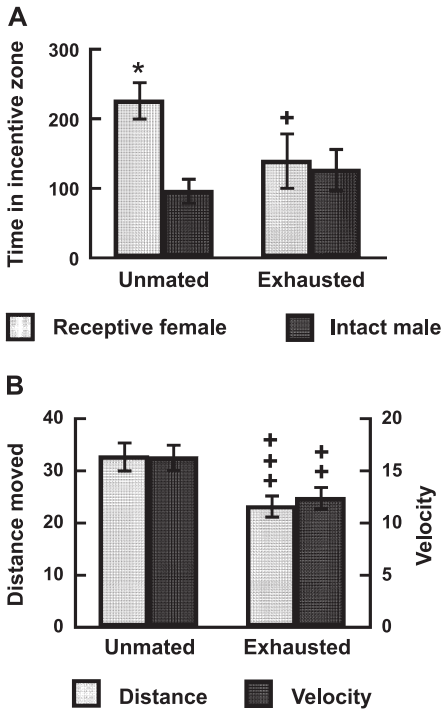

Fig. 4. (A) Time (seconds) that male rats spent in the incentive zones either without preceding sexual activity (Unmated) or after copulating for 4 h (Exhausted). (B) Distance moved (in m) during the test and mean velocity of movement (in cm/s), respectively. Data are mean ± S.E.M., $n=8$. Test duration was 10 min. Statistics: (A) Main effect of condition (unmated, exhausted): $F(1,7)=6.62$, $P<.05$; main effect of incentive: $F(1,7)=3.74$, NS; interaction Condition × Incentive: $F(1,7)=18.27$, $P<.01$. (B) Distance moved: $t(7)=6.40$, $P<.001$; velocity: $t(7)=5.90$, $P=.01$. * Different from intact male, $P<.05$; $^{+}$different from unmated, $P<.05$, $^{++}P<.01$, and $^{+++}P<.001$.

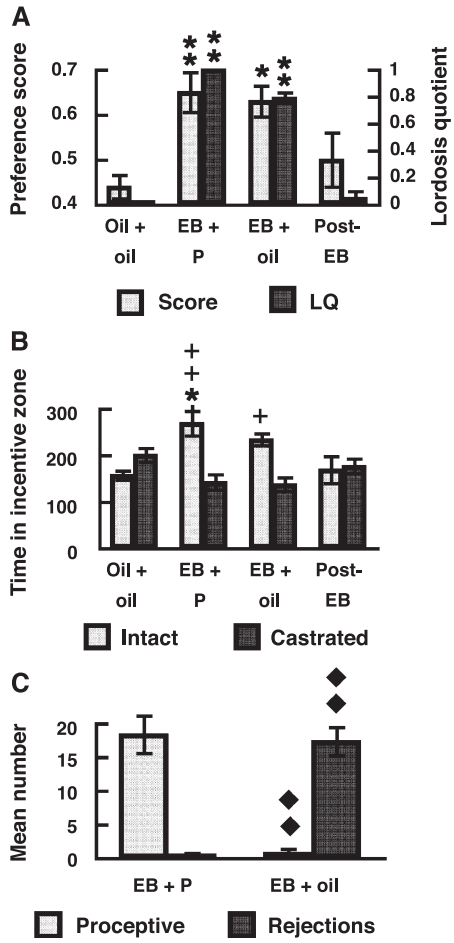

Fig. 5. Preference score (left axis) and lordosis quotient (right axis) (A), time (seconds) spent in the incentive zones (B) and number of proceptive behaviors and rejections (C) in ovariectomized female rats. The subjects were treated with oil 48 and 4 h before the first test for sexual incentive motivation (Oil + oil). Immediately after this test, receptivity was determined in a standard mating test with a sexually active male. The test lasted until 10 mounts had been observed. The following day, the females received a subcutaneous injection of estradiol benzoate, 25 μg, and 48 h later, they were injected with progesterone, 1 mg. About 4 h later, a test for sexual motivation was performed, and immediately thereafter, the females were tested for receptivity. During this test, the numbers of proceptive behaviors (hop darting, ear wiggling) and of rejections were counted. This is test EB + P. After another 48 h, the females were given an oil injection and tested in a manner identical to the preceding test 4 h later. This is test EB + oil. Ten days after the EB injection, the females were given an additional motivation and receptivity test 4 h after an injection of oil. At the first and the last tests, the females were almost totally unresponsive to the male, and only presence or absence of lordosis in response to mount was registered. Data are mean ± S.E.M., $n=8$. Duration of the test for sexual incentive motivation was 10 min. Statistics: (A) Preference score: $F(3,21)=5.27$, $P<.01$. Lordosis quotient was evaluated with Friedman's two-way ANOVA [$\chi^2(3)=23.71$, $P<.001$]. All conditions were compared with oil + oil according to the post hoc procedure recommended in Siegel and Castellan (1988). (B) Main effect of test: $F(3,21)=2.88$, NS; of incentive (intact vs. castrated male): $F(1,7)=6.95$, $P<.05$; interaction Test × Incentive: $F(3,21)=6.24$, $P<.01$. A posteriori comparisons of the interaction means were made with Tukey's HSD test. (C) Number of proceptive behaviors: $t(7)=6.86$, $P<.001$; number of rejections: $t(7)=8.86$, $P<.001$. * Different from oil + oil, $P<.01$, ** $P<.01$; $^{+}$different from the time spent in the castrated male incentive, $P<.05$, $^{++}P<.01$. ◆◆Different from EB + P, $P<.01$.

experiment is that estradiol is required for female sexual incentive motivation, whereas progesterone is not necessary. In another experiment, some females were exposed to sexually active males until the males had obtained three ejaculations. A motivation test was performed about 1 min later. Again, it was reasoned that extensive sexual activity should reduce sexual motivation. This prediction was confirmed (Fig. 6). The females did not spend more time in the vicinity of the active male compared with the castrated male. It seems, then, that the procedure adequately evaluates sexual motivation also in females.

An important feature of the procedure described here is that sexual incentive motivation remains stable over many tests. This becomes evident if data from the intact males shown in Fig. 2 are examined. Twelve tests performed regularly over a period of 2 months gave almost identical results in this group. It must be noted that these males were sexually inexperienced and that they remained so during the entire experiment. However, sexual experience does not modulate sexual incentive motivation, provided that it does not immediately precede the test (Ågmo, 2003). Also in females, sexual incentive motivation remains stable over long periods of time (Fig. 7) and is not modified by sexual

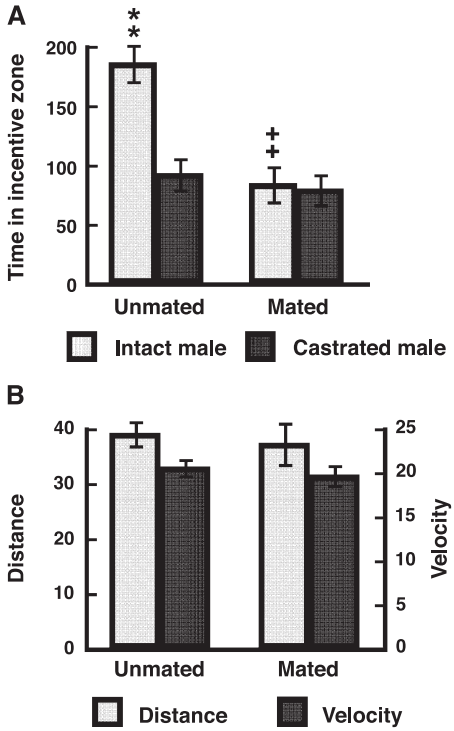

Fig. 6. (A) Time (seconds) that female rats spent in the incentive zones either without preceding sexual activity (Unmated) or after having received three ejaculations in a standard mating test (Mated). (B) Distance moved (in m) during the test and mean velocity of movement (in cm/s), respectively. The females were ovariectomized and treated with ovarian hormones, as explained in Fig. 5. Data area mean ± S.E.M., $n = 10$. Test duration was 10 min. Statistics: (A) Main effect of condition (unmated, mated): $F(1,9) = 14.95$, $P < .01$; main effect of incentive: $F(1,9) = 5.59$, $P < .05$; interaction Condition × Incentive: $F(1,9) = 5.76$, $P < .05$. Interaction means were compared using Tukey's HSD procedure, with $k = 4$. It is the results from this test that are illustrated. (B) Distance moved: $t(7) = 0.53$, NS; velocity: $t(7) = 0.75$, NS. ** Different from the castrated male, $P < .01$; ++ Different from the time spent in the intact male incentive zone when unmated, $P < .01$.

experience. The fact that motivation is stable over long periods makes it possible to employ repeated-measures designs, e.g., for drug testing. The lack of effect of sexual experience makes it possible to combine the test for incentive motivation with a test for copulatory behavior, if that should be of interest.

Assuming that the procedure indeed measures sexual motivation uncontaminated by other variables, we need to ask whether it has any predictive validity as preclinical model of sexual desire and whether it can model hypoactive and/or hyperactive sexual desire. The paucity of data as to the etiology of these disorders, as well as to the pharmacological treatment of them, makes it difficult to answer this question. There are two observations that indirectly offer some information, though.

Specific serotonin re-uptake inhibitors have a high incidence of sexual side effects in the human, as mentioned. Among these side effects is reduced sexual desire in both men and women. Moreover, some of the serotonin re-uptake inhibitors have been used for treating hyperactive sexual desire in men (see above). One study has shown that chronic, but not acute, treatment with fluoxetine reduces and eventually eliminates sexual incentive motivation in male rats in a procedure identical to ours (Matuszczyk et al., 1998). In addition, hyperactive sexual desire in men has been efficiently reduced by treatments reducing blood androgen concentrations. A drastic reduction of circulating androgens in rats has the same effect in our procedure. These observations are indicative of some correlational validity. A one-dose, one-drug study and some coincidence concerning the effects of reduced concentration of testicular hormones are certainly not enough for any definitive conclusion, but they are at least suggestive.

It has been suggested that an unusually high sexual motivation is the causative agent in men with unusually high levels of sexual activity, expressed as total sexual outlet (see above). An interesting question is whether rats with high motivation display more or more intense sexual behavior than do rats with low motivation. To determine this, data from two unpublished experiments were analyzed. In these experiments, tests for sexual incentive motivation had been performed immediately before the tests for copulatory behavior in sexually experienced males. The subjects were separated in two subgroups according to their preference score. One group had preference score above the median and the other below the median. When parameters of sexual behavior in these subgroups were compared, it was found that animals with high preference score had shorter ejaculation latency in both experiments. Differences on other parameters were not consistent (see Table 1). The specific relationship between the intensity of sexual incentive motivation and ejaculation latency was not unexpected. Others have reported that manipulations supposed to enhance sexual motivation, like observing other rats copulating or being preexposed to a receptive female (de Jonge et al., 1992; Hård and Larsson, 1969) or conditioning of stimuli predictive of sexual activity (Zamble et al., 1985, 1986), also have a specific effect on ejaculation latency. It appears then that sexual incentive motivation in our procedure

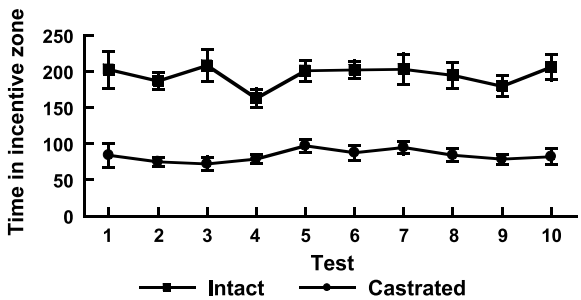

Fig. 7. Sexual incentive motivation in female rats tested 10 times at irregular intervals during a period of 3 months. The incentives were a sexually active, intact male and a castrated male. Data are mean ± S.E.M., $n = 10$. Test duration was 10 min. Statistics: test: $F(9,81) = 1.38$, NS; incentive: $F(1,9) = 28.3$, $P < .001$; interaction Test × Incentive: $F(9,81) = 1.02$, NS.

Table 1
Sexual behavior in male rats having either a preference score below (low motivation) or above the median (high motivation) in two separate experiments

Behavior parameter	Experiment 1		Experiment 2	
	Low motivation	High motivation	Low motivation	High motivation
Preference score	0.54 ± 0.01	0.72 ± 0.01***	0.60 ± 0.05	0.85 ± 0.03 **
Mount latency	83 ± 36	100 ± 52	160 ± 118	40 ± 10
Intromission latency	116 ± 52	143 ± 37	195 ± 156	100 ± 42
Ejaculation latency	521 ± 162	189 ± 24 **	464 ± 88	186 ± 46 *
Number of mounts	11 ± 4	4 ± 1	17 ± 3	6 ± 1 *
Number of intromissions	9 ± 2	6 ± 1	12 ± 2	8 ± 1
Postejaculatory interval	317 ± 39	440 ± 110	296 ± 26	260 ± 12

In Experiment 1, $n = 12$ per subgroup and $n = 6$ in Experiment 2. Latencies are in seconds. Data are mean ± S.E.M. Due to nonhomogenous error variances, comparisons were made with the Mann–Whitney U test.

* Different from low motivation, $P < .05$.

** Different from low motivation, $P < .01$.

*** Different from low motivation, $P < .001$.

predicts a fundamental component of male rat sexual behavior. Reduced ejaculation latency in rats is not necessarily equivalent to enhanced total sexual output in humans, but at least, these results show that the intensity of sexual motivation is not unrelated to the intensity of copulatory behavior. Perhaps, male rats with high preference score could be a model of hyperactive sexual desire in men.

As repeatedly mentioned above, one hypothesis concerning the origin of hypoactive sexual desire is that sexual activity has not been associated with appropriate reward, or it may even have had aversive consequences. Similar circumstances may be created in rats. Indeed, if copulation in male rats is repeatedly followed by an aversive event, sexual incentive motivation is extinguished, and the receptive female is eventually avoided (Ågmo, 2002). This conditioned extinction of sexual motivation and the ensuing reduced sexual activity could constitute a homology to hypoactive sexual disorder; that is, the rats show modifications of behavior similar to and with the same cause as those found in humans. This exciting possibility needs to be further explored. What is lacking are clinical studies of men and women diagnosed with hypoactive sexual desire disorder in which their sexual reward history is carefully examined. In addition, experimental studies in female rats administered an aversive event in association with sexual activity are badly needed because existing data are limited to the male.

The reduction of hyperactive sexual desire associated with the paraphilias through aversive conditioning previously discussed is very similar with the experiment where we associated sexual interaction with a scented female with an aversive stimulus (Ågmo, 2002). Here, then, we have an example where a therapeutic approach in the human gives results similar with those obtained in the preclinical motivation test presently described. This reinforces the notion that the test may be of predictive validity.

In this context, it may be pointed out that the procedure presented here offers a most remarkable opportunity for testing one of the hypotheses referring to the etiology of hypoactive sexual desire, as well as of the only reasonably well-documented psychological treatment. We think of the hypothesis that hypoactive sexual desire disorder appears as a result of absent sexual reward and/or frustration because of absent sexual reward. The treatment that can be tested is the orgasm consistency training. It has been shown that the affective state activated by sexual activity, which we call sexual reward, can be blocked by injections of naloxone both in male and female rats (Ågmo and Berenfeld, 1990; Ågmo and Gómez, 1993; Paredes and Martínez, 2001). Thus, it would be possible to administer naloxone before each of many tests for sexual behavior and test for progressive development of reduced sexual motivation. As mentioned, we have already shown that sex behavior associated with an aversive event eliminates sexual motivation, and this could be equivalent to the situation where frustration follows sexual activity because frustration is known to have aversive properties (e.g., Otis and Ley, 1993; Tranel, 1983, in humans, Daly, 1969; Daly and Daly, 1982, in rats). In fact, when sexual reward was inhibited by the injection of naloxone, sex behavior acquired aversive properties in both male and female rats (Ågmo and Berenfeld, 1990; Paredes and Martínez, 2001). This was explained as a consequence of the absence of reward in a situation where it is expected. This leads to the development of frustrative nonreward (Amsel, 1962).

Concerning treatment of hypoactive sexual desire, it would be possible to arrange an equivalent to orgasm consistency training in rats. Provided that sexual motivation has been reduced or extinguished by the use of one of the procedures outlined above, it could then be tested how sexual motivation returns as sexual reward is reintroduced. The amount of sexual reward could be systematically varied, different contingencies of reinforcement tested, and so on.

In view of the limited amount of both clinical and animal data available, it is not possible to determine whether the model described has correlational validity. It may be isomorphic and perhaps homologous, but these assertions require additional data before surpassing the state of suggestion.

10. Paced mating in female rats as a model

In the standard test for copulatory behavior, a male and a female are put together in a small enclosure (Ågmo, 1997). In this situation, it appears that the male controls most of the sexual interaction. However, studies in seminatural environments have shown that it is rather the female who is in control. More than 90% of sexual interactions are initiated by the female (McClintock and Adler, 1978). The male initiates about 3%. In the remaining interactions, it was difficult to determine who was the initiator. Studies in wild rats have equally shown that the female controls the pace of sexual interactions by making herself available for a short period and then disappearing in a burrow. After a short time, she reappears for a new sexual encounter, then disappears again, and so on. This may go on until the period of estrous is over (Robitaille and Bouvet, 1976).

The natural situation can easily be simulated in the laboratory. A mating arena is simply divided in two or more compartments, and openings are made in the divisions. These openings are of such a size that the small female easily can pass while the larger male cannot. The consequence is that the female can move freely within the arena while the male is confined to one part. The behavior observed in this kind of testing apparatus is frequently called paced mating. The fundamental element is that the female is able to escape to an area inaccessible to the male. At the beginning of a mating test, the female is placed in one compartment and the male in another. If and when the female enters the male compartment, sexual interaction can take place. It has repeatedly been reported that the female withdraws to her own compartment after sexual interactions. Withdrawal occurs sometimes after mounts, frequently after intromission and almost always after ejaculation. There is, then, a direct relationship between the intensity of vaginocervical stimulation received and the likelihood of female withdrawal. The time required for the female to reappear after withdrawal is also directly proportional to the amount of sensory stimulation received. It is shortest after a mount and longest after an ejaculation (Erskine, 1989). The pacing procedure has become increasingly popular, and it has been suggested that it can be employed as a procedure for evaluating sexual motivation in the female (Erskine, 1989). The latency to enter the male's compartment, calculated from the beginning of the test, as well as the time required to return to the male's compartment after withdrawals, has been proposed as measures of motivation (see Pfaff and Ågmo, 2002, for a discussion). However, there has not been any experimental study showing this to be the case. Studies of female sexual behavior in a bilevel chamber (Pfaus et al., 1999) are not adequate for analyzing the motivational aspects of paced mating because the fundamental element of pacing, the availability of a compartment to which only the female has access, was absent. It could be argued, of course, that the female could pace her interactions by running from one level of the chamber to another so fast that the male could not attain her. The same argument could be applied to any mating environment. The difference between a standard mating cage and the bilevel chamber is that running is horizontal in the former and vertical in the latter. In addition, the total surface area of the bilevel chamber is substantially smaller than that of most standard mating arenas, making it particularly difficult for the female to establish any significant distance between herself and the male. Furthermore, it is not considered that the possibility to run is sufficient for satisfying the essentials of what is normally understood by pacing. If it were, then, any mating test would be a paced-mating test. Thus, the notion that pacing was studied in the Pfaus et al. (1999) study is untenable. The results of that study have therefore no relevance for paced mating as normally understood.

In view of the potential interest of paced mating as a procedure for analyzing sexual motivation in the female, and because of the lack of data confirming or contradicting this notion, we decided to make some observations of females in varying states of sexual motivation. This was achieved by observing females during prolonged sexual interaction, supposing that the motivation to engage in sexual activities should get gradually reduced.

Those aspects of female sexual behavior that showed the largest changes from the beginning to the end of the test should be those best reflecting the intensity of motivation. It has already been shown that the time that the female stays away from the male after sexual interactions (mounts, intromission and ejaculation) gradually increases as she receives more ejaculations (Yang and Clemens, 1997). However, these studies were not pursued, or data were not presented, beyond the third ejaculation. We ended the test at the fifth ejaculation. In addition to the traditional parameters of paced mating, i.e., the latency to enter the male's compartment at the beginning of the test, durations of withdrawals from the male (called return latencies), the proportion of mounts, intromissions and ejaculations followed by withdrawal, and receptivity (the proportion of mounts provoking lordosis), we also analyzed proceptive behaviors. These are ear wiggling and hop darting. The supposed function of these behaviors is to attract the male and stimulate him to initiate mounting (Beach, 1976). Proceptive behaviors have been reported to be critical determinants of the male's initiation of sexual behavior under conditions where this is difficult, viz., sexually inexperienced males, recently castrated males or in long-term castrated males given low doses of testosterone (Hlinak and Madlafousek, 1977; Hlinak et al., 1979; Madlafousek and Hlinak, 1983; Madlafousek et al., 1976). Behaviors enhancing the likelihood that the partner will engage in sexual activity could probably be expected to have motivational significance, but this needs to be shown. Therefore, we quantified proceptive behaviors during the different phases of the sexual interactions. All females responded with lordosis to every mount in every series. Because of that, we will not further mention receptivity data.

Results show that return latencies during the initial part of the test, until and after the first ejaculation, showed the expected pattern, i.e., increase according to the intensity of sexual stimulation. During and after the fifth ejaculatory series, the latencies were generally longer but also more variable (see Fig. 8A). The return latency after a mount appeared to be prolonged, but this was due to one rat who had a latency of 18.73 min. If this rat is removed, the mean return latency of the four remaining animals that withdrew after mount was 0.58 min, very similar with that in the first series. Return latencies after intromission and ejaculation were significantly increased, though. The proportion of withdrawals did not show systematic variation between Series 1 and 5 (Fig. 8B).

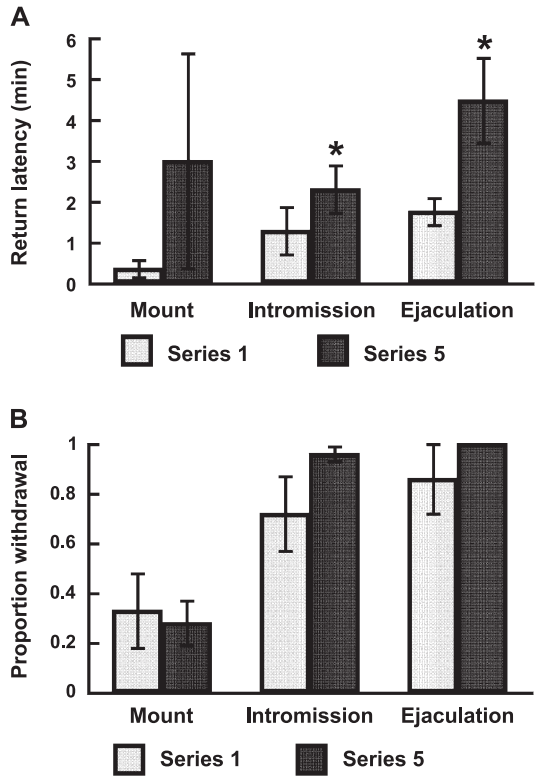

Fig. 8. Return latencies (A) and proportion of exits after different degrees of sexual stimulation (B) shown by females during a paced mating test. Subjects (Wistar rats) were ovariectomized and given the hormone treatment explained in Fig. 5. Pacing was observed in a rectangular cage (40 × 60 × 40 cm high) divided in halves lengthwise by a transparent Plexiglas partition. Three adjustable openings were located at regularly spaced distances in the bottom of the partition The openings were adjusted before each test so that the female could easily pass, while the male (Wistar) was too big to fit. For a more detailed description, see Ellingsen and Ågmo (2004). Data are mean ± S.E.M. of the individual means, $n = 7$. Statistics: Only three animals withdrew after mount in both the first and fifth series. Therefore, a repeated-measures analysis is of little value. For illustrative purposes only, it is mentioned that the mean ± S.E.M. mount return latency in the first series was 0.51 ± 0.40 vs. 0.46 ± 0.30 in the fifth for these three females. Data shown in the figure are based on all animals withdrawing after at least one mount. Intromission return latency: $t(5) = 2.77$, $P < .05$; ejaculation return latency: $t(5) = 2.88$, $P < .05$. There was no significant difference between the first and fifth series with regard to the proportion of withdrawals (all Ps>0.11). * Different from the first series, $P < .05$.

These data would suggest that neither the return latency after mount nor the proportion of withdrawals are particularly sensitive indicators of sexual motivation. We have found that the withdrawal response after a mount is a spurious phenomenon (Ellingsen and Ågmo, 2004). It is not activated by the mount but is a simple coincidence between the spontaneous movements within the mating cage and the mounting by the male. Even in the absence of sexual stimulation, the female now and then leaves the male compartment. The frequency of leaving is not enhanced by a mount, and the time she stays away is similar with the time she spends in her compartment at spontaneous withdrawal. The proportions of exits after mount, as well as mount return latency, are therefore basically measures of ambulatory activity.

The withdrawal response associated with intromission and ejaculation is activated by vaginocervical stimulation. If the pudendal and pelvic nerves are cut, then, withdrawal after intromission/ejaculation lasts no longer than after a mount (Erskine, 1992). It is known that vaginocervical stimulation activates an analgesic response (reviewed in Komisaruk and Sansone, 2003), and it has been suggested that the stimulation obtained during intromission or ejaculation may be painful (Komisaruk and Whipple, 2000). If this is true, then, the female withdraws because of pain and returns when pain is reduced or when it has dissipated entirely. Consequently, the withdrawal responses, as well as the return latency, may constitute measures of the intensity of pain and of its duration. This seems entirely unrelated to sexual motivation.

The importance of peripheral factors for determining the return latency is further substantiated by data showing that the peripheral estrogen receptor antagonist, ICI 182,780, has profound effects on them. Return latencies after intromission and ejaculation were much enhanced by the antagonist, independently of whether the subjects were primed with estradiol alone or in combination with progesterone (Clark et al., 2003). It seems, therefore, that hormone actions outside the central nervous system are important determinants of the return latencies. Because motivation is thought to be a central process, these observations argue against the use of them as indices of motivation. In sum, then, several lines of evidence make us conclude that return latencies are of questionable value in studies of sexual motivation.

Proceptive behaviors were infrequent before the female had entered the male's compartment. The frequency of these behaviors increased dramatically during the period between the female's entry into the male's compartment and his first mount. At the fifth ejaculatory series, the frequency of proceptive behaviors during this same period was reduced (see Fig. 9). Proceptive behaviors were also rather frequent during the interval between the first mount and the first intromission in the first ejaculatory series. By the fifth series, the frequency was substantially lower. The rate of proceptive behaviors during this interval could, of course, only be determined when the first mount was not an intromission. This was the case in six subjects both in the

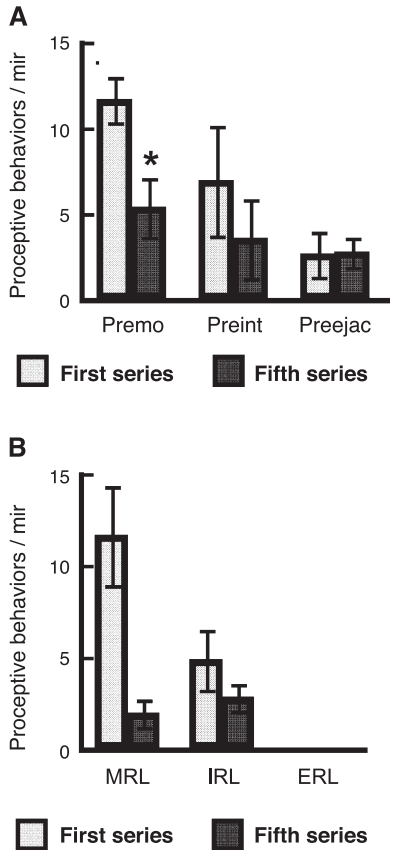

Fig. 9. Frequency of proceptive behaviors in female rats during a paced mating test. (A) Behaviors displayed in the male's compartment before the first mount (Premo), between the first mount and the first intromission in the series (Preint), and between the first intromission and the subsequent ejaculation (Preejac) in the first and fifth series. (B) Behaviors displayed in the female's compartment during the mount return latency (MRL), the intromission return latency (IRL) and ejaculation return latency (ERL) during the first and fifth series. The total number of proceptive behaviors displayed during the mount and intromission return latencies in a particular series was divided by the sum of the mount and intromission return latencies in this series, respectively. The frequency of proceptive behaviors during the ejaculation return latency was obtained by dividing the number of proceptive behaviors displayed by the time between withdrawal from the male until the return. Data are mean ± S.E.M., $n = 7$. Statistics: (A) Before mount: $t(6) = 2.72$, $P < .05$; between the first mount and the first intromission: $t(5) = 0.84$, NS; between the first intromission and the ejaculation: $t(6) = 0.13$, NS. (B) Only three females withdrew from the male's compartment after mounts during both the first and fifth series. Therefore, no statistical analysis could be made. The mean ± S.E.M. for these three females was 9.66 ± 3.23 in the first series and 2.46 ± 1.70 in the fifth. These results are mentioned for illustrative purposes only. Data shown in the figure, although, are based on all animals withdrawing after at least one mount. Proceptive behaviors during the intromission return latency: $t(5) = 1.45$, NS. There was no proceptive behavior at all during the ejaculation return latency, neither during the first nor the fifth series, and consequently, no data to analyze. * Different from the first series, $P < .05$.

first and in the fifth ejaculatory series. Between the first intromission and ejaculation, proceptive behaviors were rather infrequent whenever the female was in the male's compartment. Moreover, the frequency did not change between the first and fifth series.

During the periods that the female had withdrawn from the male following a mount, proceptive behaviors were frequent during the first series and rare during the fifth. The frequency was somewhat lower during the intromission return latencies than during the mount return latencies, but changes between first and fifth series were similar. During the ejaculation return latency, the females did not display any proceptive behaviors at all, neither after the first nor after the fifth ejaculation.

Proceptive behaviors were most frequent during the initial stages of sexual interaction. Actually, the highest frequency of proceptive behaviors were found before sexual interaction had begun, between the female's entry into the male's compartment and his first mount, then followed by the period before the first intromission. When, sexual interaction had been firmly established, proceptive behaviors became less frequent. This coincides nicely with the notion that proceptive behaviors are helpful for stimulating the male to initiate mounting and to persist mounting until intromission is achieved. The frequency of proceptive behaviors during the initial stages of sexual interaction was clearly reduced between the first and the fifth series. This suggests that they may constitute a measure of sexual motivation because the latter can be expected to be reduced as sexual interaction proceeds. Proceptive behaviors became less frequent in each series as soon as the male had intromitted, and they were entirely absent during the period the female had withdrawn from the male following ejaculation. The frequency of the late proceptive behaviors did not change between the first and fifth series, and this makes it doubtful whether they really are indicators of motivation. It seems, then, that proceptive behaviors emitted early during sexual interaction may be used as indicators of sexual motivation, whereas the meaning of the late proceptive behaviors is unknown.

This analysis shows that the paced-mating test does not offer an abundance of data useful for assessing female sexual motivation. The frequency of proceptive behaviors early during the test seems to be the only parameter that has any possible motivational significance. There is at least one problem with this idea, though. In the experiment summarized in Fig. 5, female rats displayed a significant preference for an intact male over a castrated male even at a test where proceptive behaviors were almost totally absent. On the contrary, the frequency of rejections at that test was high. The preference score was no different from a test where the females showed much proceptive behaviors and almost no rejections. At difference to proceptivity, receptivity seems to be correlated with sexual incentive motivation. At tests where the females were not receptive, they showed no preference for the intact male. There is, then, reason to believe that sexual receptivity and sexual motivation covary in response to ovarian hormones. However, they do not covary in response to recent sexual activity. While sexual incentive motivation is reduced after three ejaculations, receptivity remains unchanged, as mentioned above. Only

further studies could clarify the apparently complex relationship between proceptivity, rejections and motivation.

The data presented here do not suggest that paced mating is a particularly suitable preclinical model of sexual desire. This is probably due to the fact that the sequence of approach–avoidance constituting paced mating is heavily influenced by peripheral factors, the critical one most likely being vaginocervical stimulation and the aversive/painful consequences of it. Moreover, it seems that the procedure is in no way isomorphic to sexual behavior in women. Rather, it seems to represent a quite species-typical pattern of behavior. Copulation in women is normally not a sequence of approach–avoidance based upon painful/aversive vaginocervical stimulation. It is also doubtful whether it may be homologous. Low sexual motivation in female rats can probably be achieved by treating ovariectomized females with low doses of estradiol and/or progesterone. This has been done, and the consequence is that some females are not sexually receptive (no lordosis), thereby making adequate testing impossible. This problem was solved in some studies by assigning return latencies to nonreceptive females who did not pace, either the maximum before cut-off (Fadem et al., 1979) or simply a 0 (Gilman and Hitt, 1978). Such procedures make it impossible to know how the pacing females actually behaved. A more recent study (Brandling-Bennett et al., 1999) using real data showed that receptive females present an almost constant pacing behavior independently of hormone dose. In a group of 33 animals, 14 (42%) were receptive after treatment with unesterified estradiol, 2 μg, at 24 and 12 h before testing, and progesterone, 1 mg, 4 h before. In other conditions, treatment was either large single doses of estradiol benzoate, followed by varying doses of progesterone or repeated administration of estradiol benzoate alone. After these treatments, most of the subjects (>82%) were receptive. The only difference between these treatments with regard to pacing behavior was that unesterified estradiol + progesterone produced longer return latencies after ejaculation than the other treatments did. Interestingly, the frequency of proceptive behaviors turned out to be hormone dependent. These data show that hormone treatments having very different effects on receptivity and proceptivity have essentially the same effects on pacing behavior.

In another series of experiments (Xiao and Becker, 1997), females were made receptive by sequential implantation of estradiol and progesterone into the ventromedial nucleus of the hypothalamus, and a few hours before testing, estradiol was implanted either into the striatum or into the nucleus accumbens. In the striatum, estradiol enhanced the proportion of exits. Unfortunately, the data do not allow us to determine exit after what: mount, intromission or ejaculation. In the accumbens, estradiol enhanced return latencies. Again, it is not possible to determine after which kind of sexual contact return latencies were longer. The estrogen receptor antagonist ICI 182,780 had effects opposite to those of estradiol in animals given systemic injections of estrogen+ progesterone. The interpretation of these observations is unclear, but they could suggest that estrogens indeed modulate some aspect of pacing. Nevertheless, the effects obtained after the intracerebral administration of estradiol or an estrogen receptor antagonist were small compared with those obtained after the manipulation of peripheral estrogen receptors (Clark et al., 2003). The importance of peripheral events for paced-mating behavior could suggest that it may be a model of female sexual arousal disorder, dyspareunia and, perhaps, vaginismus rather than of sexual desire disorders.

There is no way to determine whether paced mating has correlational validity. Only two published pharmacological studies have employed this procedure (Ellingsen and Ågmo, 2004; Guarraci and Clark, 2003), and the drugs employed are of no relevance to hypoactive sexual desire disorder. There are also two abstracts employing mice in a pacing procedure (Bradshaw et al., 2002, 2003), but again, they are not relevant to the problems at hand here.

To summarize, it can only be said that paced mating is neither isomorphic nor homologous to human disorders of sexual desire. Its correlational validity remains untested. It does not seem to be the preclinical model of choice. Furthermore, it has been suggested that the mechanisms behind pacing behavior have evolved to assure maximum probability of fertilization (Hale et al., 2003). The appropriate temporal patterning of intromissions is important for fertility in some species of rodents, but there is no equivalent phenomenon in the human female. Therefore, it is far from evident that paced mating is an adequate model of human sexual motivation. In fact, it is uncertain whether it offers any advantage over simple evaluations of receptivity.

The preceding discussions are limited to an analysis of the appropriateness of paced mating and other procedures as preclinical models of sexual desire in the human. Although some procedures appear less adequate than others are for that purpose, they may constitute invaluable instruments for elucidating neurobiological mechanisms of sexual behavior. Moreover, we have limited the analysis to rodent, essentially rat, models. It is not evident that rodents are the most suitable animals for preclinical models of sexual desire. As was pointed out many years ago (Beach, 1979), primate studies may be far more informative. However, preliminary drug tests are mostly performed on rodents, and there is far more data available on rat sexual behavior than on any other species. For these reasons, we excluded primates and other nonrodent species from this review.

11. Conclusions

Epidemiological studies have shown that sexual desire disorders are common, particularly in women, but also in men. In women, the typical disorder seems to be hypoactive sexual desire, whereas men may suffer both from this and from hyperactive sexual desire. Psychological treatments are time consuming, and the outcome is uncertain. This is the

known case for the short term. With regard to long-term outcome of psychological treatments, close to nothing is known. Moreover, most psychological treatments require the participation of the partner. The willingness of the partner to invest time and effort in a treatment program is not always granted, and the problems for those not having a stable partner are still worse. Therefore, it is very likely that many individuals would prefer a reliable pharmacological treatment without side effects. The systematic development of such treatments requires undoubtedly a good preclinical model. Search for an efficient pharmacological treatment would greatly benefit from some knowledge as to the etiology of the desire disorders. An animal model that could contribute to this knowledge would be most desirable and highly useful. Ideally, the model should be relevant for males as well as for females, and for low as well as for high sexual desire. We have presented data suggesting that the sexual incentive motivation test originally developed by Meyerson and Lindström (1973) and later adapted by us (Ågmo, 2003, Ellingsen and Ågmo, 2004) may represent an acceptable model. A final evaluation of it is not possible at the present stage because of lack of clinically efficient pharmacological treatments. Paced-mating behavior does not seem to be a promising model. It is questionable whether it offers any valuable information that is not obtained in a simple test of receptivity. Standard mating tests in males may be useful, but this needs to be demonstrated.

The importance of learning for the etiology of sexual desire disorders is not known. We have suggested that conditioning may play a pivotal role. Consequently, a good preclinical model should be able to distinguish the effects of various learning contingencies on sexual motivation from each other. The model presented here may do that.

References

Abel GG, Osborn CA. Behavioural therapy treatment for sex-offenders. In: Rosen I, editor. Sexual deviation, 3rd ed. Oxford (UK): Oxford Univ. Press; 1996. p. 382–98.

Abel GG, Rouleau JL. The nature and extent of sexual assault. In: Marshall WL, Laws DR, Barbaree HL, editors. Handbook of sexual assault. New York: Plenum; 1990. p. 9–20.

Ågmo A. Male rat sexual behavior. Brain Res Protoc 1997;1:203–9.

Ågmo A. Sexual motivation. An inquiry into events determining the occurrence of sexual behavior. Behav Brain Res 1999;105:129–50.

Ågmo A. Copulation-contingent aversive conditioning and sexual incentive motivation in male rats: evidence for a two-stage process of sexual behavior. Physiol Behav 2002;77:425–35.

Ågmo A. Unconditioned sexual incentive motivation in the male Norway rat (*Rattus norvegicus*). J Comp Psychol 2003;117:3–14.

Ågmo A, Berenfeld R. Reinforcing properties of ejaculation in the male rat: role of opioids and dopamine. Behav Neurosci 1990;104:177–82.

Ågmo A, Ellingsen E. Relevance of non-human animal studies to the understanding of human sexuality. Scand J Psychol 2003;44:291–9.

Ågmo A, Gómez M. Sexual reinforcement is blocked by infusion of naloxone into the medial preoptic area. Behav Neurosci 1993;107:812–8.

Ahlenius S, Larsson K, Svensson L. Further evidence for an inhibitory role of central 5-HT in male rat sexual behavior. Psychopharmacology 1980;68:217–20.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington (DC): Author; 1980.

American Psychiatric Association L. Diagnostic and statistical manual of mental disorders (DSM-III-R). 3rd ed., revised. Washington (DC): Author; 1987.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): 1995.

Amsel A. Frustrative nonreward in partial reinforcement and discrimination learning: some recent history and a theoretical extension. Psychol Rev 1962;69:306–28.

Arafat I, Cotten W. Masturbation practices of males and females. J Sex Res 1974;10:293–307.

Arnal A, Llario R, Gil MD. Estudio epidemiológico sobre la prevalencia de disfunciones sexuales en la comunidad valenciana. Psicothema 1995; 7:95–104.

Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. J Clin Psychiatry 1998;59:112–5.

Atmaca M, Kuloglu M, Tezcan E, Semercioz A. The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study. Int J Impot Res 2002;14:502–5.

Audet N, Trudel G. L'inventaire des comportements sexuels. Rev Modif Comport 1985;15:20–30.

Bancroft J. Testosterone therapy for low sexual interest and erectile dysfunctions in men: a controlled study. Br J Psychiatry 1984;14:146–51.

Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med 2001;16:266–75.

Baumeister RF, Catanese KR, Vohs KD. Is there a gender difference in strength of sexual drive? Theoretical views, conceptual distinctions, and a review of relevant literature. J Pers Soc Psychol 2001;5:242–73.

Beach FA. A review of physiological and psychological studies of sexual behavior in mammals. Physiol Rev 1947a;27:240–307.

Beach FA. Evolutionary changes in the physiological control of mating behavior in mammals. Psychol Rev 1947b;54:297–315.

Beach FA. Sexual attractivity, proceptivity, and receptivity in female mammals. Horm Behav 1976;7:105–38.

Beach FA. Animal models of human sexuality. CIBA Foundation Symposium, new series 62. Sex, hormones and behaviour. Amsterdam: Excerpta; 1979. p. 113–43.

Bentler PM, Peeler WH. Models of female orgasm. Arch Sex Behav 1979;8:405–23.

Bindra D. A motivational view of learning, performance, and behavior modification. Psychol Rev 1974;81:199–213.

Bindra D. A theory of intelligent behavior. New York: Wiley; 1976.

Bindra D. How adaptive behaviour is produced: a perceptual–motivational alternative to response reinforcement. Behav Brain Sci 1978;1:41–52.

Bogner HR, Gallo JJ. Are higher rates of depression in women accounted for by differential symptom reporting? Soc Psychiatry Psychiatr Epidemiol 2004;39:126–32.

Bortolotti A, Parazzini F, Colli E, Landoni M. The epidemiology of erectile dysfunction and its risk factors. Int J Androl 1997;20:323–34.

Bozman AW, Beck JG. Covariation of sexual desire and sexual arousal: the effects of anger and anxiety. Arch Sex Behav 1991;20:47–60.

Bradford JMW, Pawlaka A. Double-blind placebo crossover study of cyproterone-acetate in the treatment of the paraphilias. Arch Sex Behav 1993;22:383–402.

Bradshaw AA, Gordon M, Gordon J, Luine V. Dopamine and paced sexual behavior in female mice. Soc Neurosci 2002;482.3.

Bradshaw A, Gautreaux C, Luine VN. The effects of apomorphine on sexual behavior of female C57 mice. Soc Neurosci 2003;281.13.

Brandling-Bennett EM, Blasberg ME, Becker JB. Paced mating behavior in female rats in response to different hormone priming regimens. Horm Behav 1999;35:144–54.

Bremer J. Asexualization: a follow-up study of 244 cases. Oslo: Oslo University Press; 1958.

Briken P, Hill A, Berner W. Pharmacotherapy of paraphilias with long-acting agonists of luteinizing hormone-releasing hormone: a systematic review. J Clin Psychiatry 2003;64:890–7.

Bullough VL. Science in the bedroom. A history of sex research. New York: Basic Books; 1994.
Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. J Androl 1992;13:297–304.
Carlton PL. Theories and models in psychopharmacology. In: Lipton MA, DiMascio A, Killam KF, editors. Psychopharmacology: a generation of progress. New York: Raven; 1978. p. 553–61.
Chambless DL, Baker MJ, Baucom DH, Beutler LE, Calhoun KS, Crits-Christoph P, et al. Update on empirically validated therapies: II. Clin Psychologist 1998;51:3–16.
Clark AS, Guarraci FA, Megroz AB, Porter DM, Henderson LP. The display of sexual behaviors by female rats administered ICI 182,780. Horm Behav 2003;43:454–64.
Contreras JL, Ågmo A. Sensory control of the male rat's copulatory thrusting patterns. Behav Neural Biol 1993;60:234–40.
Daly HB. Aversive properties of partial and varied reinforcement during runway acquisition. J Exp Psychol 1969;81:54–60.
Daly HB, Daly JT. A mathematical model of reward and aversive nonreward: its application in over 30 appetitive learning situations. J Exp Psychol Gen 1982;111:441–80.
Davis SR, Tran J. Testosterone influences libido and well being in womern. Trends Endocr Metab 2001;12:33–7.
de Jonge FH, Oldenburger WP, Louwerse AL, van de Poll NE. Changes in male copulatory behavior after sexual exciting stimuli: effects of medial amygdala lesions. Physiol Behav 1992;52:327–32.
Eckman J, Meltzer JD, Latané B. Gregariousness in rats as a function of familiarity of environment. J Personal Soc Psychol 1969;11:107–14.
Edwards DA, Einhorn LC. Preoptic and midbrain control of sexual motivation. Physiol Behav 1986;37:329–35.
Eichel EW, Eichel JD, Kule S. The technique of coital alignment and its relation to female orgasmic response and simultaneous orgasm. J Sex Marital Ther 1988;14:129–41.
Ellingsen E, Ågmo A. Sexual incentive motivation and paced sexual behavior in female rats after treatment with drugs modifying dopaminergic neurotransmission. Pharmacol Biochem Behav 2004;77:431–45.
Erskine MS. Solicitation behavior in the estrous female rat: a review. Horm Behav 1989;23:473–502.
Erskine MS. Pelvic and pudendal nerves influence the display of paced mating behavior in response to estrogen and progesterone in the female rat. Behav Neurosci 1992;106:690–7.
Everaerd W, Laan E. Drug treatments for women's sexual disorders. J Sex Res 2000;37:195–204.
Everitt BJ. Sexual motivation: a neural and behavioral analysis of the mechanisms underlying appetitive and copulatory responses of male rats. Neurosci Biobehav Rev 1990;14:217–32.
Everitt BJ, Stacey P. Studies of instrumental behavior with sexual reinforcement in male rats (*Rattus norvegicus*): II. Effects of preoptic area lesions, castration, and testosterone. J Comp Psychol 1987;101:407–19.
Fadem BH, Barfield RJ, Whalen RE. Dose–response and time–response relationships between progesterone and the display of patterns of receptive and proceptive behavior in the female rat. Horm Behav 1979;13:40–8.
Fout JC. Forbidden history: the state, society and the regulation of sexuality in modern Europe. Chicago (IL): University of Chicago Press; 1992.
Fugl-Meyer AR, Sjögren-Fugl-Meyer K. Sexual disabilities, problems and satisfaction in 18–74 year old Swedes. Scand J Sexol 1999;2:79–105.
Gebhard PH. Factors in marital orgasm. J Soc Issues 1966;22:88–95.
Giambra LM, Martin CE. Sexual daydreams and quantitative aspects of sexual activity: some relations for males across adulthood. Arch Sex Behav 1977;6:497–505.
Gilman DP, Hitt JC. Effects of gonadal hormones on pacing of sexual contacts by female rats. Behav Biol 1978;24:77–87.
Gitlin MJ, Suri R, Altshuler L, Zuckerbrow-Miller J, Fairbanks L. Bupropion sustained release as a treatment for SSRI-induced sexual side effects. J Sex Marital Ther 2002;28:131–8.
Greenberg DM, Bradford JMW. Treatment of the paraphilic disorders: a review of the role of the selective serotonin reuptake inhibitors. Sex Abus J Treat Res 1997;9:349–60.
Greenberg DM, Bradford JMW, Curry S, O'Rourke A. A comparison of treatment of paraphilias with three serotonin reuptake inhibitors: a retrospective study. Bull Am Acad Psych Law 1996;24:525–32.
Guarraci FA, Clark AS. Amphetamine modulation of paced mating behavior. Pharmacol Biochem Behav 2003;76:505–15.
Guay AT. Decreased testosterone in regularly menstruating women with decreased libido: a clinical observation. J Sex Marital Ther 2001;27:513–9.
Hale TM, Heaton JPW, Adams MA. A framework for the present and future development of experimental models of female sexual dysfunction. Int J Impot Res 2003;15(Suppl. 5):S75–9.
Hård E, Larsson K. Effects of precoital exposure of male rats to copulating animals upon subsequent mating performances. Anim Behav 1969;17:540–1.
Harris G. After 5 years, rivals emerge ready to give Viagra a fight. New York: New York Times Company; 2003. C1 [August 21].
Hawton K, Catalan J, Fagg J. Low sexual desire: sex therapy results and prognostic factors. Behav Res Ther 1991;29:217–24.
Heiman JR. Psychologic treatment for female sexual dysfunction: are they effective and do we need them? Arch Sex Behav 2002;31:445–50.
Hetta J, Meyerson BJ. Sexual motivation in the male rat. A methodological study of sex-specific orientation and the effects of gonadal hormones. Acta Physiol Scand 1978;1–67.
Hlinak Z, Madlafousek J. Female precopulatory behaviour as a determinant of sexual activity in male rats. Act Nerv Super 1977;19:242–3.
Hlinak Z, Madlafousek J, Mohapelova A. Initiation of copulatory activity in castrated male rats injected with critically adjusted doses of testosterone. Horm Behav 1979;13:9–20.
Hurlbert DF. A comparative study using orgasm consistency training in the treatment of women reporting hypoactive sexual desire. J Sex Marital Ther 1993;19:41–55.
Hurlbert DF, Apt C, Rabehl SM. Key variables to understanding female sexual satisfaction—an examination of women in nondistressed marriages. J Sex Marital Ther 1993a;19:154–65.
Hurlbert DF, White LC, Powell RD, Apt C. Orgasm consistency training in the treatment of women reporting hypoactive sexual desire: an outcome comparison of women-only groups and couples-only groups. J Behav Ther Exp Psychiatry 1993b;24:3–13.
Hurlbert DF, Apt C, Hurlbert MK. Sexual characteristics, treatment compliance and the effectiveness of orgasm consistency training in the treatment of women reporting hypoactive sexual desire. Can J Hum Sex 1995;4:15–23.
Hurlbert DF, Apt C, Hurlbert MK, Pierce AP. Sexual compatibility and the sexual desire-motivation relation in females with hypoactive sexual desire disorder. Behav Modif 2000;24:325–47.
Hurtazo HA, Paredes RG, Ågmo A. Inactivation of the medial preoptic area/anterior hypothalamus (MPOA/AH) reduces sexual incentive motivation in male rats. Soc Neurosci Abstr. 2003;404.6.
Kafka MP. Hypersexual desire in males: an operational definition and clinical implications for males with paraphilias and paraphilia-related disorders. Arch Sex Behav 1997;26:505–26.
Kafka MP. The paraphilia-related disorders: nonparaphilic hypersexuality and sexual compulsivity/addiction. In: Leiblum SR, Rosen RC, editors. Principles and practice of sex therapy 3rd ed. New York: Guilford; 2000. p. 471–503.
Kafka MP, Hennen J. The paraphilia-related disorders: an empirical investigation of nonparaphilic hypersexuality disorders in outpatient males. J Sex Marital Ther 1999;25:305–19.
Kafka MP, Prenkty R. A comparative study of nonparaphilic sexual addictions and paraphilias in men. J Clin Psychiatry 1992a;53:345–50.
Kafka MP, Prenkty R. Fluoxetine treatment of nonparaphilic sexual addictions and paraphilias in men. J Clin Psychiatry 1992b;53:358.
Kaplan HS. The sexual desire disorders. Dysfunctional regulation of sexual motivation. New York: Brunner/Mazel; 1995.
Kennedy SH, McCann SM, Masellis M, McIntyre RS, Raskin J, McKay G,

et al. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. J Clin Psychiatry 2002;63:181–6.
Kinsey AC, Pomeroy WB, Martin CE. Sexual behavior in the human male. Philadelphia: Saunders; 1948.
Kinsey AC, Pomeroy WB, Martin CE, Gebhard PH. Sexual behavior in the human female. Philadelphia: Saunders; 1953.
Klein R, Sturm H. Viagra: a success story for rationing? Health Aff 2002; 21:177–87.
Komisaruk BR, Sansone G. Neural pathways mediating vaginal function: the vagus nerves and spinal cord oxytocin. Scand J Psychol 2003;44: 241–50.
Komisaruk BR, Whipple B. How does vaginal stimulation produce pleasure, pain, and analgesia? In: Fillingim RB, editor. Sex, gender and pain. Seattle (WA): IASP; 2000. p. 109–34.
Kondo Y, Sachs BD. Disparate effects of small medial amygdala lesions on noncontact erection, copulation, and partner preference. Physiol Behav 2002;75:1–5.
Kubin M, Wagner G, Fugl-Meyer AR. Epidemiology of erectile dysfunction. Int J Impot Res 2003;15:63–71.
Ladwig KH, Marten-Mittag B, Formanek D, Dammann G. Gender differences of symptom reporting and medical health care utilization in the German population. Eur J Epidemiol 2000;16:511–8.
Latané B. Gregariousness and fear in laboratory rats. J Exp Soc Psychol 1969;5:61–9.
Latané B, Glass DC. Social and nonsocial attraction in rats. J Pers Soc Psychol 1968;9:142–6.
Latané B, Joy V, Meltzer J, Lubell B, Cappell H. Stimulus determinants of social attraction in rats. J Comp Physiol Psychol 1972;79:13–21.
Latané B, Edwards J, Steele C, Walton D. Social attraction among and between albino and hooded rats. Bull Psychon Soc 1973;2:20–2.
Laumann EO, Gagnon JH, Michael RT, Michaels S. The social organization of sexuality. Sexual practices in the United States. Chicago: University of Chicago Press; 1994.
Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999;281:537–44.
Laws DR, Osborn CA. How to build and operate a behavioral laboratory to evaluate and treat sexual deviance. In: Greer JG, Stuart IR, editors. The sexual aggressor: current perspectives on treatment. New York: Van Nostrand; 1983. p. 293–335.
Levine SB. A modern perspective on nymphomania. J Sex Marital Ther 1982;8:316–24.
Lewin B, Fugl-Meyer K, Helmius G, Lalos A, Månsson SA. Sex i Sverige. Om sexuallivet i Sverige 1996. Stockholm: Folkhälsoinstitutet; 1998.
Lexchin J. Lifestyle drugs: issues for debate. Can Med Assoc J 2001;164: 1449–51.
Lief HI. Current thinking of the orgasm experience. Med Aspects Hum Sex 1980;14:55–62.
Liu YC, Salamone JD, Sachs BD. Lesions in medial preoptic area and bed nucleus of stria terminalis: differential effects on copulatory behavior and noncontact erection in male rats. J Neurosci 1997;17: 5245–53.
Lobo RA, Rosen RC, Yang HM, Block B, van der Hoop RG. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 2003;79: 1341–52.
LoPiccolo J. Diagnosis and treatment of male sexual dysfunction. J Sex Marital Ther 1985;11:215–32.
LoPiccolo J. Paraphilias. Nord Sexol 1992;10:1–14.
LoPiccolo J, Friedman JM. Broad-spectrum treatment of low sexual desire: integration of cognitive, behavioral, and systemic therapy. In: Leiblum SR, Rosen RC, editors. Sexual desire disorders. New York (NY): Guilford; 1988. p. 107–44.
LoPiccolo J, Stock WE. Treatment of sexual dysfunctions. J Consult Clin Psychol 1986;54:158–67.
López HH, Olster DH, Ettenberg A. Sexual motivation in the male rat: the role of primary incentives and copulatory experience. Horm Behav 1999;38:176–85.
Lorenz K. The comparative method in studying innate behavior patterns. Symp Soc Exp Biol 1950;4:221–68.
Madlafousek J, Hlinak Z. Importance of female's precopulatory behaviour for the primary initiation of male's copulatory behaviour in the laboratory rat. Behaviour 1983;86:237–49.
Madlafousek J, Hlinak Z, Beran J. Decline of sexual behavior in castrated male rats: effects of female precopulatory behavior. Horm Behav 1976;7:245–52.
Maletzky BM. Self-referred versus court-referred sexually deviant patients: success with assisted covert sensitization. Behav Ther 1980;11:306–14.
Malmnäs CO. Monoaminergic influences on testosterone-activated copulatory behavior in the castrated male rat. Acta Physiol Scand 1973; (Suppl. 395):1–128.
Masters WH, Johnson VE. Human sexual inadequacy. Boston: Little, Brown and Co; 1970.
Matthews TJ, Grigore M, Tang L, Doatz M, Kow LM, Pfaff DW. Sexual reinforcement in the female rat. J Exp Anal Behav 1997;68:399–410.
Matuszczyk J, Larsson K, Erikson E. The selective serotonin reuptake inhibitor fluoxetine reduces sexual motivation in male rats. Pharmacol Biochem Behav 1998;60:527–32.
McCabe MP. A program for the treatment of inhibited sexual desire in males. Psychotherapy 1992;29:288–96.
McCabe MP. Evaluation of a cognitive behavior therapy program for people with sexual dysfunction. J Sex Marital Ther 2001;27:259–71.
McClintock MK, Adler NT. The role of the female during copulation in wild and domestic Norway rats (*Rattus norvegicus*). Behaviour 1978;67:67–96.
McGinnis MY, Montana R, Lumia AR. Effects of hydroxyflutamide in the medial preoptic area or lateral septum on reproductive behaviors in male rats. Brain Res Bull 2002;59:227–34.
McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride. Int J Impot Res 1999;11:241–5.
Mendelson SD, Pfaus JG. Level searching: a new assay of sexual motivation in the male rat. Physiol Behav 1989;45:337–41.
Meyer WJ, Collier C, Emory E. Depo-Provera treatment for sex offending behavior: an evaluation of outcome. Bull Am Acad Psych Law 1992; 20:249–59.
Meyerson BJ. Central nervous monoamines and hormone induced estrus behavior in the spayed rat. Acta Physiol Scand 1964a;(Suppl. 241): 1–32.
Meyerson BJ. The effects of neuropharmacological agents on hormone-activated estrus behavior in ovariectomized rats. Arch Int Pharmacodyn Ther 1964b;150:4–33.
Meyerson BJ, Lindström LH. Sexual motivation in the female rat. A methodological study applied to the investigation of the effect of estradiol benzoate. Acta Physiol Scand 1973;(Suppl. 389):1–80.
Meyerson BJ, Eliasson M, Hetta J. Sex-specific orientation in female and male rats: development and effects of early endocrine manipulation. Adv Biosci 1979;25:451–60.
Mitrany D. Lifestyle drugs—determining their value and who should pay. Pharmacoeconomics 2001;19:441–8.
Modell JG, Katholi CR, Modell JD, DePalma L. Comparative sexual side effects of SSRIs and bupropion. Clin Pharmacol Ther 1997;61:476–87.
Nathan SG. The epidemiology of the DSM-III psychosexual dysfunctions. J Sex Marital Ther 1986;12:267–81.
O'Donahue W, Dopke CA, Swingen DN. Psychotherapy for female sexual dysfunction: a review. Clin Psychol Rev 1997;17:537–66.
Otis J, Ley R. The effects of frustration induced by discontinuation of reinforcement on force of response and magnitude of the skin conductance response. Bull Psychon Soc 1993;31:97–100.
Paredes RG. Medial preoptic area/anterior hypothalamus and sexual motivation. Scand J Psychol 2003;44:203–12.
Paredes RG, Alonso A. Sexual behavior regulated (paced) by the female induces conditioned place preference. Behav Neurosci 1997;111: 123–8.

Paredes RG, Baum MJ. Altered sexual partner preference in male ferrets given excitotoxic lesions of the preoptic area anterior hypothalamus. J Neurosci 1995;15:6630.
Paredes RG, Martínez I. Naloxone blocks place preference conditioning after paced mating in female rats. Behav Neurosci 2001;115:1363–7.
Paredes RG, Vázquez B. What do female rats like about sex? Paced mating. Behav Brain Res 1999;105:117–27.
Paredes RG, Highland L, Karam P. Socio-sexual behavior in male rats after lesions of the medial preoptic area: evidence for reduced sexual motivation. Brain Res 1993;618:271–6.
Paredes RG, Tzschentke T, Nakach N. Lesions of the medial preoptic area/anterior hypothalamus (MPOA/AH) modify partner preference in male rats. Brain Res 1998;813:1–8.
Pfaff DW. Motivational concepts: definitions and distinctions. In: Pfaff DW, editor. The physiological mechanisms of motivation. New York: Springer; 1982a. p. 3–24.
Pfaff DW. Neurobiological mechanisms of sexual motivation. In: Pfaff DW, editor. The physiological mechanisms of motivation. New York (MA): Springer; 1982b. p. 287–317.
Pfaff DW. Drive. Neurobiological and molecular mechanisms of sexual motivation. Cambridge (MA): MIT Press; 1999.
Pfaff DW, Ågmo A. Reproductive motivation. In: Pashler H, Gallistel R, editors. Steven's handbook of experimental psychology. Learning, Motivation, and Emotion, vol. 3. New York: Wiley; 2002. p. 709–36.
Pfaff DW, Lewis C, Diakow C, Keiner M. Neurophysiological analysis of mating behavior as hormone-sensitive reflexes. Prog Physiol Psychol 1973;5:253–97.
Pfaus JG, Smith WJ, Coopersmith CB. Appetitive and consummatory sexual behaviors of female rats in bilevel chambers: I. A correlational and factor analysis and the effects of ovarian hormones. Horm Behav 1999;35:224–40.
Pierce AP. The coital alignment technique (CAT): an overview of studies. J Sex Marital Ther 2000;26:257–68.
Piletz JE, Segraves KB, Feng YZ, Maguire E, Dunger B, Halaris A. Plasma MHPG response to yohimbine treatment in women with hypoactive sexual desire. J Sex Marital Ther 1998;24:43–54.
Portillo W, Paredes RG. Sexual and olfactory preference in noncopulating male rats. Physiol Behav 2003;80:155–62.
Quinsey VL, Marshall WL. Procedures for reducing inappropriate sexual arousal: an evaluation review. In: Greer JG, Stuart IR, editors. The sexual aggressor. Current perspectives on treatment. New York: Van Nostrand; 1983. p. 267–89.
Quinsey VL, Harris GT, Rice ME, Lalumiere ML. Assessing treatment efficacy in outcome studies of sex offenders. J Interpers Violence 1993; 8:512–23.
Rice ME, Harris GT, Quinsey VL. Evaluation of an institution-based treatment program for child molesters. Can J Program Eval 1991;6:111–29.
Riley A, Riley E. Controlled studies on women presenting sexual drive disorder: I. Endocrine status. J Sex Marital Ther 2000;26:269–83.
Robinson IE, Jedlicka D. Change in behavior and attitudes of college students from 1965 to 1980. J Marriage Fam 1982;44:237–40.
Robitaille JA, Bouvet J. Field observations on the social behaviour of the Norway rat, *Rattus norvegicus* (Berkenhout). Biol Behav 1976;1: 289–308.
Rodríguez-Manzo G, Fernández-Guasti A. Reversal of sexual exhaustion by serotonergic and noradrenergic agents. Behav Brain Res 1994;62: 127–34.
Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999;19:67–85.
Sachs BD. Role of striatal penile muscles in penile reflexes, copulation, and induction of pregnancy in the rat. J Reprod Fertil 1982;66:433–43.
Sachs BD. Erection evoked in male rats by airborne scent from estrous females. Physiol Behav 1997;62:921–4.
Sachs BD. Contextual approaches to the physiology and classification of erectile function, erectile dysfunction, and sexual arousal. Neurosci Biobehav Rev 2000;24:541–60.
Sarrel PM. Effects of hormone replacement therapy on sexual psychophysiology and behavior in postmenopause. J Women's Health Gend-Based Med 2000;9(Suppl. 1):S25–32.
Sarwer DB, Durlak JA. A field trial of the effectiveness of behavioral treatment for sexual dysfunctions. J Sex Marital Ther 1997;23:87–97.
Schiaivi RC, Karstaedt A, Schreiner-Engel P, Mandeli J. Psychometric characteristics of individuals with sexual dysfunctions and their partners. J Sex Marital Ther 1992;18:219–30.
Schover LR, LoPiccolo J. Treatment effectiveness for dysfunctions of sexual desire. J Sex Marital Ther 1982;8:179–97.
Schreiner-Engel P, Schiari PC, White D, Ghizzani A. Low sexual desire in women: the role of reproductive hormones. Horm Behav 1989;23: 211–34.
Segraves RT. Antidepressant-induced sexual dysfunction. J Clin Psychiatry 1998;59(Suppl. 4):48–54.
Segraves KB, Segraves RT. Hypoactive sexual desire disorder: prevalence and comorbidity in 906 subjects. J Sex Marital Ther 1991;17:55–8.
Segraves RT, Croft H, Kavoussi RJ, Ascher JA, Batey SR, Foster VJ, et al. Bupropion sustained release (SR) for the treatment of hypoactive sexual desire disorder (HSDD) in nondepressed women. J Sex Marital Ther 2001;27:303–16.
Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. Psychosom Med 1987; 49:397–409.
Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. Psychosom Med 1985;47:339–51.
Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 2000;343:682–8.
Siegel S, Castellan NJ. Non parametric statistics for the behavioral sciences. New York: McGraw-Hill; 1988.
Sigusch V. The neosexual revolution. Arch Sex Behav 1998;27:331–59.
Smith ER, Lee RS, Schnur SL, Davidson JM. Alpha2-adrenoceptor antagonists and male sexual behavior: II. Erectile and ejaculatory reflexes. Physiol Behav 1987;41:15–9.
Spallanzani L. Expériences pour servir à l'histoire de la génération. Genève, Switzerland: Barthelemi Chirol; 1784.
Spector I, Carey M. Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. Arch Sex Behav 1990; 19:389–408.
Spector IP, Leiblum SR, Carey MP, Rosen RC. Diabetes and female sexual function: a critical review. Ann Behav Med 1993;15:257–64.
Stoléru S, Redouté J, Costes N, Lavenne F, Le Bars D, Dechaud H, et al. Brain processing of visual sexual stimuli in men with hypoactive sexual desire disorder. Psychiat Res Neuroimaging 2003;124:67–86.
Stone CP, Barker RG, Tomilin MI. Sexual drive in potent and impotent male rats as measured by the Columbia obstruction apparatus. J Genet Psychol 1935;47:33–48.
Stuart FM, Hammond DC, Pett MA. Inhibited sexual desire in women. Arch Sex Behav 1987;16:91–106.
Thornton A. Changing attitudes toward family issues in the United States. J Marriage Fam 1989;51:873–93.
Tranel DT. The effects of monetary incentive and frustrative nonreward on heart rate and electrodermal activity. Psychophysiology 1983;20: 652–7.
Treit D. Animal models for the study of anti-anxiety agents: a review. Neurosci Biobehav Rev 1985;9:203–22.
Trudel G. Review of psychological factors in low sexual desire. Sex Marital Ther 1991;6:261–72.
Trudel G, Boulos L, Matte B. Dyadic adjustment in couples with hypoactive sexual desire. J Sex Educ Ther 1993;19:31–6.
Trudel G, Aubin S, Matte B. Sexual behaviors and pleasure in couples with hypoactive sexual desire. J Sex Educ Ther 1995;21:210–6.
Trudel G, Fortin C, Matte B. Sexual interaction and communication in couples with hypoactive sexual desire. Scand J Behav Ther 1997;26: 49–53.
van Minnen A, Kampman M. The interaction between anxiety and sexual

functioning: a controlled study of sexual functioning in women with anxiety disorders. Sex Relationship Ther 2000;15:47–57.
Vega-Matuszczyk J, Larsson K. Role of androgen, estrogen and sexual experience on the female rat's partner peference. Physiol Behav 1991; 50:139–42.
Vega-Matuszczyk J, Larsson K. Sexual orientation and sexual motivation of the adult male rat. Physiol Behav 1993;53:747–50.
Vega-Matuszczyk J, Larsson K. Experience modulates the influence of gonadal hormones on sexual orientation of male rats. Physiol Behav 1994;55:527–31.
Vega-Matuszczyk J, Appa RS, Larsson K. Age-dependent variations in the sexual preference of male rats. Physiol Behav 1994;55:827–30.
Ventegodt S. Sex and quality of life in Denmark. Arch Sex Behav 1998;27:295–307.
Verbrugge LM. Gender and health: an update on hypotheses and evidence. J Health Soc Behav 1985;26:156–82.
Vogelgesang M. Psychotherapie des Exhibitionismus: Theorien zur Psychogenese und therapeutische Leitlinien. Psychotherapeut 1999;44: 288–99.
Vreeburg JTM. Induction of ear wiggling in the estrous female rat by gonadectomized rats treated with androgens and estrogens. Horm Behav 1985;19:231–6.
Vroege JA, Gijs L, Hengeveld MW. Classification of sexual dysfunctions: towards DSM-V and ICD-11. Compr Psychiatry 1998;39:333–7.
Waldinger MD. Use of psychoactive agents in the treatment of sexual dysfunction. CNS Drugs 1996;6:204–16.
Waldinger MD, Zwinderman AH, Olivier B. Antidepressants and ejaculation: a double-blind, randomized, placebo-controlled, fixed-dose study with paroxetine, sertraline and nefazodone. J Clin Psychopharmacol 2001;21:293–7.
Wantoch H. Die bisher in Schweiz gesammelten Erfahrungen über die Kastration von Sexualverbrechern. Arch Kriminol 1935;96:78–80.
Warnock JK. Female hypoactive sexual desire disorder. CNS Drugs 2002;16:745–53.
Warnock JK, Bundren JC, Morris DW. Female hypoactive sexual disorder: case studies of physiologic androgen replacement. J Sex Marital Ther 1999;25:175–82.
Whalen RE. Hormone-induced changes in the organization of sexual behavior in the male rat. J Comp Physiol Psychol 1964;57:175–82.
Whalen RE, Beach FA, Kuehn RE. Effects of exogenous androgen on sexually responsive and unresponsive male rats. Endocrinology 1961; 68:373–80.
Willner P. Behavioural models in psychopharmacology. In: Willner P, editor. Behavioural models in psychopharmacology: theoretical, industrial and clinical perspectives. Cambridge (UK): Cambridge Univ. Press; 1991. p. 3–18.
Wilson GD, Lang RJ. Sex differences in sexual fantasy patterns. Pers Individ Differ 1981;2:343–6.
World Health Organization RJ. International statistical classification of diseases and related health problems, 1989 revision. Geneva: Author; 1989.
Xiao L, Becker JB. Hormonal activation of the striatum and the nucleus accumbens modulates paced mating behavior in the female rat. Horm Behav 1997;32:114–24.
Yang LY, Clemens LG. Function of intromissions and intromission–return latency of female rats during paced sexual behavior. Physiol Behav 1997;61:889–94.
Young PT. Motivation and emotion. A survey of the determinants of human and animal activity. New York: Wiley; 1961.
Zamble E, Hadad GM, Mitchell JB, Cutmore TRH. Pavlovian conditioning of sexual arousal: first- and second-order effects. J Exp Psychol, Anim Behav Processes 1985;11:598–610.
Zamble E, Mitchell JB, Findlay H. Pavlovian conditioning of sexual arousal: parametric and background manipulations. J Exp Psychol, Anim Behav Processes 1986;12:403–11.
Zetterberg HL. Sex i Sverige: huvudavsnittet av undersökningen om sexuallivet i Sverige företagen av SIFO. Stockholm: Aldus/Bonniers; 1969.