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Review article

Sexual incentive motivation, sexual behavior, and general arousal: Do rats and humans tell the same story?

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ABSTRACT

Sexual incentive stimuli activate sexual motivation and heighten the level of general arousal. The sexual motive may induce the individual to approach the incentive, and eventually to initiate sexual acts. Both approach and the ensuing copulatory interaction further enhance general arousal. We present data from rodents and humans in support of these assertions. We then suggest that orgasm is experienced when the combined level of excitation surpasses a threshold. In order to analyze the neurobiological bases of sexual motivation, we employ the concept of a central motive state. We then discuss the mechanisms involved in the long- and short-term control of that state as well as those mediating the momentaneous actions of sexual incentive stimuli. This leads to an analysis of the neurobiology behind the interindividual differences in responsivity of the sexual central motive state. Knowledge is still fragmentary, and many contradictory observations have been made. Nevertheless, we conclude that the basic mechanisms of sexual motivation and the role of general arousal are similar in rodents and humans.

1. Introduction

Sexual motivation is a concept used to explain interindividual as well as intraindividual variations in response to sexually relevant stimuli. Thus, an individual responding strongly to a sexual stimulus is considered to be highly motivated while an individual showing no or weak response is considered to have a low level of sexual motivation. A convenient operational definition of sexual motivation would then be "responsivity to sexually relevant stimuli". Responsivity can be measured in many ways, for example by determining the intensity of approach to an individual of the opposite sex in rodents, or the enhancement of genital blood flow in men and women when exposed to sexually relevant stimuli.

With the exception of self-stimulation (masturbation), sexual behavior requires at least one partner. Therefore, most sexual activities are preceded by approach to a potential partner. With potential partner is understood any individual that is attractive to the actor and who might be willing to engage in sexual activity once approach has been accomplished. After completed approach, physical interaction with the partner and eventually copulation may become possible.

We will present evidence showing that distant sexual stimuli as well as stimuli provided by the partner during precopulatory and copulatory interaction will enhance general arousal. The main purpose of this review is to demonstrate that enhanced general arousal is a fundamental part of sexual interactions. In fact, we will propose that the experience of orgasm is heavily dependent on enhanced general arousal. Earlier accounts of sexual motivation and sexual interactions ignored the role of general arousal (e.g. Basson, 2000; Hayes, 2011), thereby weakening the explanatory power of these accounts. Instead, we will show that including general arousal as one determinant of the intensity of sexual motivation and a significant contributor to the subjective experience of orgasm greatly enhances the explanatory power of any model of sexual incentive motivation. Furthermore, it appears that the relationship between sexual motivation, sexual acts and general arousal is similar in rodents and humans. The behavioral consequences of this may be different, though, because of the social conventions influencing human sexual behavior (see Gagnon and Simon, 2002).

Sexual motivation and general arousal must somehow be materialized in the brain. Presumably, neural activity determines the level both of sexual motivation and general arousal. Neither of these is constant but

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varies over time within the individual (see Pfaff, 1982, 2006, for analyses of this issue). We will soon see, for example, that exposure to a sexual incentive will immediately enhance sexual motivation. It can be assumed that incentive-induced changes in the brain are the cause of this. The identification of these brain changes would reveal the neural workings of sexual motivation. Likewise, the changes in general arousal associated with exposure to incentives must be due to changes in nervous activity.

Besides the variation in sexual motivation and general arousal within the individual, there are vast variations between individuals. Those following the clinical literature may have noticed that some individuals consider themselves as asexual, completely lacking motivation for partnered sexual activities (de Oliveira et al., 2021). Others suffer from compulsive sexual behavior or hypersexuality (Asiff et al., 2018). These interindividual differences must also have a neural substrate. A considerable part of this review is dedicated to a summary of the known causes of intra- and interindividual differences in sexual motivation, and the possible relationship to the dynamics of general arousal.

Before proceeding with an examination of the role of general arousal in sexual motivation and behavior and the neurobiology of these, we will provide clear definitions of the main concepts. Without such definitions, any scientific analysis would be futile.

2. Definitions

2.1. Sexual approach behavior

The sexual approach behaviors are highly flexible both in rodents and humans, and they are determined by the context. In experimental setups, rats can approach a potential partner by walking or running towards it, or the subject may be required to navigate a maze, or cross an electric grid, or press a lever to gain access to a partner (reviewed in Pfaff and Ågmo, 2002). The human may employ an infinite variety of behavior patterns when sexually approaching another individual. These patterns include verbal messages, body gestures and facial expressions (e.g. Brak-Lamy, 2015; Vannier and O'Sullivan, 2011). None of these behaviors involves the genitals, whereas sexual behaviors always do. Because of this basic difference between sexual approach behaviors and sexual behavior sensu stricto, it is convenient to treat them as separate entities in the sequence of behavior patterns involved in sexual interactions.

A convenient definition of sexual approach is "*any activity leading to reduction of the physical distance to a potential mate to the point that the individuals are in physical contact*". The fact that behaviors involved in sexual approach are highly variable precludes any definition in terms of specific motor patterns. A consequence of the variability in behaviors used for accomplishing approach is that we cannot distinguish sexual approach from other kinds of approaches by observing motor patterns. The stimulus activating approach behavior can obviously be informative, but not always conclusive. If a rat approaches a food pellet, we can reasonably assume that there are no sexual intentions behind, but if it approaches another rat, even of opposite sex, we cannot know if the rat is in search of social or sexual contact. Rats are gregarious, and are strongly attracted to other rats both of the same and the opposite sex (e.g. Latané, 1969; Sloan and Latané, 1974). In order to distinguish sexual from social approach we must wait until we have determined what happens after successful approach. If the rats start to copulate, we can conclude that the approach was sexual, and if they don't even try to copulate, approach was social. There are other ways to distinguish different kind of approaches (Ågmo et al., 2004; Spiteri and Ågmo, 2006), but here it is sufficient to draw attention to the fact that approach behaviors are not specific for any particular motive.

2.2. Sexual (copulatory) behavior

Sexual behavior can be defined as "*any action leading to sexual reward. Sexual reward is a state of positive affect activated by physical stimulation of the genitalia or mental representations of such stimulation*"(Ågmo, 2007, p. 3). It must be noted that this definition does not refer to the sex or the species of the individual providing the genital stimulation. It does not even refer to a partner at all. This means that solitary sex (masturbation), as well as sex in groups, are included. Furthermore, humans may obtain sexual reward in the absence of genital stimulation. Women may experience orgasm through the exclusive use of sexual fantasies, and such orgasms have the same endocrine and neural manifestations as orgasms induced by mechanical stimulation of the clitoris (Whipple et al., 1992; Wise et al., 2016). There is also anecdotal evidence suggesting that men can achieve orgasms through fantasies (Klumbies and Kleinsorge, 1950). Thus, in humans, mental representations of genital stimulation may replace actual stimulation. It is uncertain whether other animals can produce similar mental representations.

The need for engagement of the genitals to consider a behavior as sexual does not always imply that the individual's own genitals are involved. For example, the provider of cunnilingus or fellatio, or the one being penetrated in anal sex, must be considered to execute a sexual behavior, even though the own genitals are not (necessarily) mechanically stimulated.

In rodents, sexual behavior is nothing more than a series of somatic and visceral reflexes. In both males and females these reflexes are activated by tactile stimulation of the posterior part of the body. In females, the rump and flanks are crucial (Pfaff et al., 1973), whereas the preputial region is essential in males (Contreras and Ågmo, 1993). The reflexive nature of the copulatory motor patterns make them highly stereotyped within the species (Dewsbury, 1972). In non-human primates, sexual behaviors are less stereotyped than in rodents (Dewsbury and Pierce Jr, 1989). Human sexual behavior is entirely different, in the way that the motor patterns involved are extremely variable. Genital stimulation may be achieved in many different ways, and various body openings may be used to that end (Kinsey et al., 1948, 1953). Whereas sexual interactions usually are limited to penile-vaginal intercourse in non-human animals, this activity is only one of many possibilities in humans. In fact, human sexual behavior is only limited by the creativity and acrobatic proficiency of the participants.

2.3. General arousal

The activity level of organisms varies over time. During sleep, the organism shows reduced muscular activity, and the electroencephalographic record is distinctly different from that obtained during the awake state (e.g. Stickgold and Walker, 2009). The reactivity to weak environmental stimuli is reduced. Awakening is associated with increased muscular activity and reactivity to environmental stimuli. Demanding situations, such as a premier league football match, may enhance activity and reactivity to very high levels, not only in the players but also in the spectators. The variations in activity and reactivity are explained by reference to the concept of arousal (e.g. Andrew, 1974). Originally proposed by Moruzzi and Magoun (1949), the level of general arousal is determined by the activity in a diffuse brain stem system, the ascending reticular activating system. This system is still believed to be of fundamental importance (Jones, 2020; Pfaff, 2006; Pfaff et al., 2008).

An everlasting issue is whether arousal is general or if there are specific arousals controlling reactivity to groups of stimuli rather than to all stimuli. Furthermore, there is some confusion with regard to differentiating arousal from motivation, in the way that the many specific arousals described actually may be manifestations of motivation (Ågmo, 2011). Even the proponents of multiple arousals recognize that their use of the arousal concept is "akin to incentive motivation" (e.g. Jing et al., 2009, p. 408). In the present review, we consistently consider arousal as general, affecting the responsivity to all stimuli in a similar way. An acceptable definition of arousal would then be: Enhanced arousal causes an animal to display greater motor activity, to be more alert to

environmental stimuli, and to show greater emotional reactivity (Pfaff et al., 2002). It can also lead to a series of physiological changes typical of heightened activity in the sympathetic nervous system. Among those are increased heart rate and blood pressure, pupil dilation, release of corticosteroids from the adrenal cortex and of adrenalin from the adrenal medulla (e.g. Gomez et al., 2016; Wang et al., 2018). The many observable manifestations of general arousal, in both rodents and humans, have been used to accumulate a substantial amount of experimental data on the mutual relationship between sexual behaviors and arousal. We will integrate these data in the incentive motivational model of sex.

3. Historical note on hypotheses concerning the activation of sexual motivation and behavior

After having introduced the basic concepts, we can now turn to an analysis of the workings of sexual motivation and its relationship to general arousal. Without an explicit model of sexual motivation and the sequence of events constituting sexual behavior, any serious analysis of the influence of general arousal would be impossible. To put this analysis in context, it is convenient to trace the historical origins of current notions. It will become evident that an incentive motivational approach was used in the early writings on sexual behavior, long before the term incentive motivation had been invented. Furthermore, it was recognized that partnered sex always is preceded by approach to another individual. These notions were prominent in the extremely influential instinct theory exposed by William McDougall and in the writings of the founder of psychoanalysis, Sigmund Freud. We will briefly describe the essential elements of these two approaches. We do that not only as an expression of respect for these pioneers, but also for showing that current notions are the result of an almost linear evolution. Still more important, it may illustrate how concepts from widely different approaches may have more in common than could be expected a priori.

3.1. McDougall' sexual instinct

As far as we know, the British psychologist William McDougall was the first to explicitly include sexual approach in his outline of the nature of sexual behavior. Even though McDougall's extravagant instinct theory is now largely forgotten, there are some notions which have survived and appear in contemporary thought. According to McDougall, all instincts can be considered as complex, innately organized, psychophysical dispositions, consisting of a cognitive, an affective and a conative part (McDougall, 1926). The cognitive part consists of perception and evaluation of stimuli relevant to each instinct. This evaluation leads to an affective reaction that can or cannot be experienced as an emotion. In the case of the sexual instinct, the emotion would be lust, according to McDougall. Finally, the conative part of the instinct will eventually lead to an organized course of action, i.e. motor output. Conation is understood as the mental processes of volition, i.e. acts of the will, leading to the striving towards some goal. The goal-directed actions were included in the conative part of McDougall's initial instinct model. In his later writings, McDougall concluded that the conative part cannot be clearly distinguished from the affective or emotional part. Furthermore, the motor output simply serves to discharge the instinctive excitement, and should not be included in the conative part (McDougall, 1950). Concerning the sexual instinct, the motor activities are described in the following way:

> …the general character of these innately prescribed actions seems clear, namely, approach to the object which excites the instinct, followed by close bodily contact, and the specifically sexual movements; that is to say, like many other instincts, it impels not merely to some one simple action, but to a train of actions which naturally succeed one another as the situation develops (McDougall, 1914, p. 73).

As will become evident, the ordered sequence of events constituting partnered sexual behavior (approach – body contact – sexual movements) described by McDougall is still perfectly valid. Concerning the source of the sexual instinct, McDougall is not particularly explicit. He excludes gonadal secretions and does not mention any other somatic influence. It appears that an external stimulus is required, because he writes "….the perception by the eye of the human form is one, and the principal one, of several innately provided roads to excitement of the sex instinct" (McDougall, 1914, p. 74). The appropriate stimulus is able to release an almost infinite amount of "psychic energy", which can lead to intense activity directed towards the satisfaction of the instinct (McDougall, 1913). It appears that McDougall anticipated later incentive motivational theories when proposing that external stimuli (incentives) are the primary source for activating the sexual instinct.

The innate stimulus – response connections needed for the activation of the sexual instinct is at the basis of McDougall's hypothesis. We will see that unconditioned responses to specific stimuli indeed are essential for the activation of sexual behavior in non-human animals. There is, however, no reason to believe that they are so for humans, contrary to McDougall's claims. Nevertheless, the inclusion of approach to a potential mate in addition to actual copulation in the sexual instinct model was an innovative idea. Still today, most models or accounts of sexual behavior ignores the events preceding copulation.

3.2. Sigmund Freud's notion of "Sexualtrieb"

Any account of sexual motivation would be incomplete without mentioning the visionary approach created by Freud more than 100 years ago. Often criticized or despised, his analysis of motivation has nevertheless had enormous influence during the last century, and many of the fundamental elements are still valid. There are, evidently, many notions that are outdated or manifestly erroneous, but as we will show below, some are still invaluable.

The following account is based upon Freud's seminal paper from 1915 (Freud, 1915) and on his theory of sexuality in its original version (Freud, 1905). First, however, a note on terminology. The English translation (Freud, 1957) of the title of the 1915 paper is "Instincts and their vicissitudes" whereas the original German title is "Triebe und Triebschicksale". The literal translation of "Triebe" should be "drives". However, since Freud's use of the word resembled the use of the English word "instinct", James Strachey (the translator) might have considered instinct as a more appropriate translation than drive. Nevertheless, this translation has been criticized and some psychoanalysts maintain that the correct word indeed should be "drive" (e.g. Frank, 2003; Mills, 2004). It has also been argued that a still better translation would be motive (Frank, 2004), a word that was much used by Freud himself (e.g. Freud, 1917). We will follow that suggestion.

Motives are made up of four elements:

1. The source (die Quelle). The source is a somatic process, either chemical or physical, occurring in the internal organs. The source impinges on the central nervous system in the form of a drive stimulus. According to Freud, the study of the sources as well as the factors activating these sources lies outside the scope of psychology.
2. The thrust or pressure (der Drang). This is the amount of force or the demand for work exercised by the motive. It is presumably dependent on the intensity of the drive stimulus.
3. The aim or goal (das Ziel). The aim is to eliminate the drive stimulus. This can be achieved in many different ways, meaning that any motive can lead to a variety of different actions.
4. The object (das Objekt) is anything that can reduce or eliminate the drive stimulus, thereby satisfying the motive. There is no obligatory connection between the source and the object.

There are two additional things that need to be mentioned. Whereas the source of the motive is entirely internal, its intensity can be

reinforced by external events. In the case of the sexual motive, it can be reinforced by stimulation of erotogenic zones, for example. Tactile or thermic stimulation of some skin areas will be efficient. Sexually exciting visual stimuli also contribute to enhance the intensity of the drive. Since such stimuli are received by the eyes, the eye is also an erotogenic zone. Likewise, if sound enhances the sexual drive, then the ear is an erotogenic zone. The important point here is that the intensity of the internally originated drive can be enhanced by external stimuli of many kinds. Finally, mental representations of sexually relevant events can also contribute to drive intensity.

Of particular importance in this extremely simplified summary of the Freudian account of motivation or drive is the independence of source and object, and the flexibility in the ways to achieve the aim. With regard to sexual motivation, that means that any object, be it an individual of the same or of the opposite sex, of the same or of a different species, or even an inanimate object, can satisfy the source. It is also noteworthy that Freud acknowledges that the drive intensity is determined by an interaction between internal states and external or imaginary stimuli. This is exactly the main point in contemporary incentive motivation theories. Furthermore, an unlimited variation in motor patterns can be used to achieve the motive's aim. Likewise, because there is no obligatory connection between source and aim, sexual behavior may be used for satisfying non-sexual motives. Both these characteristics of Freud's analysis of motivation are directly relevant for contemporary analyses of sexuality.

3.3. Frank Beach

Whereas McDougall and Freud had no interest in sexual functions in non-human animals, Beach elaborated a model of sexual motivation based on studies in rodents, mainly rats. His 1956 chapter on male rat sexual motivation (Beach, 1956) was extremely influential during several decades, and is still frequently cited. Although Beach discussed motivation in several other papers, none has been as prominent as that one. Therefore, we will only refer to the 1956 paper here.

In line with everyone else at the time, Beach ignored the sexual approach behaviors and focused instead on how mounting is activated. To that end, he proposed a sexual arousal mechanism (SAM), described in the following way: The main function of the SAM is to increase the male's sexual excitement to such a pitch that the copulatory threshold is attained (Beach, 1956, p. 20). It has been argued that "sexual excitement" probably can be interpreted as the intensity of sexual motivation (Ågmo, 2011). However, the SAM is only one of two mechanisms determining copulatory behavior. To account for the fact that male rats not only mount females, but also achieve intromissions and eventually ejaculate, Beach proposed a second mechanism, the "intromission and ejaculation mechanism" (IEM) to be responsible both for erection, penile insertion (intromission) and ejaculation. It works in this way to activate the reflex of ejaculation: "One possible explanation is that the state of sexual excitement is progressively increased by the occurrence of successive intromissions until the ejaculatory threshold is reached. Alternatively, it might be supposed that time is the important variable, and repeated intromissions simply maintain the necessary level of excitement until ejaculation occurs" (Beach, 1956, p. 24). It turned out that both alternatives are true. Both the sensory stimulation provided by penile insertion and time are important for ejaculation (Larsson, 1960).

The important question here is whether Beach's "excitement" refers to specific facilitation of the reflexes of mounting, intromission and ejaculation or if he refers to some kind of generalized excitement, equivalent to what we here call general arousal. It is not possible to determine, but below we will show that general arousal indeed facilitates ejaculation in male rats.

Beach's use of the expression "arousal" in the SAM is problematic, because he clearly refers to what now would be called motivation. Unfortunately, the confound between arousal and motivation has infected parts of the psychological literature, and the terms are sometimes used as synonyms (Ågmo, 2008). Nevertheless, his main contribution to our understanding of sexual motivation was the much less noticed fact that he rejected an internal origin. Beach made it very clear that sexual motivation is active only in the presence of an external stimulus. "When he encounters a receptive female, the male animal may or may not become sexually excited, but it is most unlikely that in the absence of erotic stimuli he exists in a constant state of undischarged tensions" (Beach, 1956, p. 5). This point of view coincides entirely with McDougall, but only partially with Freud. The latter accepted that external stimuli could enhance sexual motivation, while not being indispensable. In that way, Beach anticipated later incentive motivation theories.

4. The incentive motivation model

4.1. General

Incentive motivation theory have become influential among the more recent approaches to the study of motivation (see Dickinson and Balleine, 2002). There are many different hypotheses about the operation of incentives and how they may relate to activity in the brain (reviewed in Berridge, 2001), but the one we have found most appropriate for analyses of sexual motivation was elaborated by Dalbir Bindra in several seminal contributions (Bindra, 1969, 1974, 1976, 1978).

An outline of an explicit incentive motivational approach to sexual activities was first presented by Frederick Toates (1986). A more elaborate model appeared several years later (Toates, 2009). Several other incentive-based models of sexual motivation have been published (Bancroft et al., 2009; Bancroft and Janssen, 2000; Both et al., 2007; Hayes, 2011; Janssen, 2011; Laan and Both, 2008). All these models are focused on human sexual motivation and they largely ignore the considerable amount of solid knowledge that has been accumulated in the field of non-human sex behavior. There is no fundamental reason to believe that the basic principles of sexuality should be more dissimilar between humans and other animals than the principles of learning or the mechanisms underlying eating and drinking. Animal data have made invaluable contributions to these fields. Regarding sexual motivation, there is an abundant animal literature addressing many fundamental issues about the behavioral manifestations of this motivation. The description of the behavioral events leading up to sexual interactions as well as these interactions themselves is far more detailed and reliable in non-human animals than in humans (see e.g. Le Moëne and Ågmo, 2019). The simple fact that the non-human data stem from direct observation and systematic experiments whereas most of the human data concerning sexual behavior come from self-reports and questionnaires makes the former more convincing.

An incentive motivation model based on ideas derived from studies of sexual motivation in non-human animals, particularly rodents, have been found to be most helpful for analyses of sexual motivation and its behavioral manifestations, from the sexual approach behaviors to the aftereffects of sex. The model has been described in some detail elsewhere (Ågmo, 1999, 2007, 2011). The sequence of events from the appearance of a sexually relevant stimulus until the cessation of sexual activity is illustrated in Fig. 1. In anticipation of the following sections, we have included potential effects of general arousal.

4.2. The model in action

As soon as a stimulus has been detected and determined to be of sexual relevance, approach behaviors will be activated. In rodents, this is essentially an automatic process, whereas cognitive evaluation of the context as well as of the appropriateness of the stimulus will play a major role in humans. Once approach has been accomplished, sexual behavior may be initiated. The transition from approach to actual sexual behavior is not always straightforward, and many approaches will be aborted before any sexual activity has been initiated. In case the transition is successful and sexual behaviors are executed, these will eventually lead

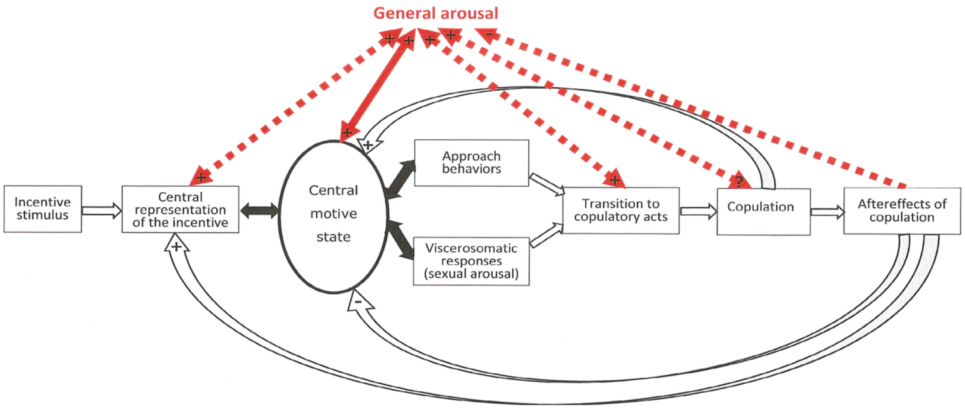


Fig. 1. The model of sexual incentive motivation. Empty arrows show unidirectional relationships whereas filled arrows illustrates reciprocal relationships. The curved arrows represents feedback systems. The part in red shows the modulatory influence of general arousal and the reciprocal relationship between arousal and the various elements of the sequence of sexual behavior. It must be noted that sexual incentive stimuli are first registered by the sense organs, then transformed into action potentials and eventually elaborated to a percept, which may be given the meaning of sexual incentive. All these processes are included in the box labeled "central representation of the incentive". For further details, see text. +, excitation. -, inhibition.

to orgasm (in humans) or to a state of positive affect in non-human animals (see Le Moëne and Ågmo, 2019). Whether the human experience of orgasm has any equivalence in other animals is not known. It has been proposed that female rats may have such an experience (Pfaus et al., 2016), but others find its existence questionable, even in non-human primates (Levin, 2017). Interestingly, the fascination with female orgasm has no counterpart with regard to male orgasm. The question of whether male non-human animals experiencer orgasm or not has attracted no attention, perhaps because it is erroneously supposed that ejaculation and orgasm are inevitably associated. Anorgasmic ejaculation in men has been reported many times (e.g. Kobayashi et al., 2009), making it evident that these events are separate. Regardless of the universality of the experience of orgasm, sexual behavior leads to affective consequences.

In both rodents and humans, all sexual encounters will eventually end. In humans, sexual activity usually ends after male orgasm and after a variable number of orgasms in women (Kinsey et al., 1948, 1953; Masters and Johnson, 1966). The exact cause of cessation of sexual activity is not known, but postejaculatory detumescence in men makes continuation of penile-vaginal intercourse difficult. Other sexual activities may persist, but eventually also they will end. Orgasm in women does not necessarily end sex, and many women are multiorgasmic. It rather appears that sexual activity is ended because sexual motivation has declined to a level below the threshold needed for maintaining such activity. One possible explanation is negative alliesthesia caused by the execution of sexual acts (Le Moëne and Ågmo, 2019). In male rodents, the behavioral event ending a copulatory encounter has been thought to be ejaculation. Data from male rats observed in a seminatural environment have shown that the probability of ending sexual interactions is equal after mount, intromission or ejaculation (Chu and Ågmo, 2015b). Female rats may copulate with different partners throughout the period of behavioral estrus (Chu and Ågmo, 2014). It is possible that negative alliesthesia also works in male rats, whereas the female seems to be sexually active as long as her brain is exposed to appropriate amounts of ovarian hormones. However, females subjected to intense sexual activity in forced copulation tests will avoid male mount attempts and show reduced receptivity, but this is considered to be a consequence of vaginal pain and not of reduced motivation (Komisaruk and Whipple, 2000).

5. General arousal and sexual motivation

5.1. The sexual incentive stimulus enhances general arousal

There is an enormous amount of evidence showing that sexual incentives have the non-surprising effect of increasing sexual arousal. However, few studies have evaluated the effects of sexually relevant stimuli on general arousal. Nevertheless, classical arousal responses, such as blood pressure, heart rate and the galvanic skin response show changes that are indicative of heightened general arousal during exposure to sexual incentives (Finke et al., 2017; Sarlo and Buodo, 2017).

Sexually relevant stimuli increase ambulatory activity in male and female rats (Mendelson and Pfaus, 1989). Likewise, the locomotor response to a neutral olfactory stimulus predicting access to a sexually receptive female is much enhanced following classical conditioning of an odor – copulation association (see Fig. 2). Insofar as ambulatory activity can be considered an indicator of general arousal as suggested by Pfaff et al. (2008), this shows that the odor gradually increases arousal as it acquires sexual incentive properties. Furthermore, exposure to a sexually active individual of the opposite sex causes an immediate increase in arterial blood pressure and heart rate in male and female rats (Saito et al., 2001; Terada et al., 2003).

We conclude this section by proposing that enhanced general arousal caused by sexual incentives contributes to the activity in the sexual central motive state. A consequence is enhanced sexual responses to sexually relevant stimuli.

5.2. Sexual approach behaviors and general arousal

One way to show that enhanced general arousal actually stimulates responses to sexually relevant stimuli would be to expose individuals to arousal-enhancing stimuli with no sexual relevance, and simultaneously expose them to sexually relevant stimuli. Several studies in humans and rats have done exactly this. Many psychology textbooks mention an experiment in which young men encountered a young woman either on a shaky suspension bridge or on a regular bridge. The men crossing the suspension bridge found the woman more attractive than did the men crossing the regular bridge. Similarly, the threat of imminent electric shock increased attractiveness of an opposite sex confederate. Moreover, the men in the fear-inducing contexts reported more sexual imagery than control subjects (Dutton and Aron, 1974). The observation that arousal-enhancing situations, regardless of the procedure used for increasing arousal, enhance physical attractiveness of opposite, but not same sex individuals, have been replicated many times and seems to be a robust phenomenon (Foster et al., 1998). Although ratings of increased attractiveness are not necessarily indicative of sexual motivation, the fact that it was specific for persons of the opposite sex may suggest that general arousal had increased the responsiveness of the sexual central motive state, thereby facilitating approach behaviors.

The effects of sexually irrelevant, arousal-enhancing stimuli or events on sexual approach behavior have not been studied in rodents. Instead, general arousal has been modified with drugs. Provided that locomotor activity is an appropriate indicator of arousal level, drugs enhancing or reducing locomotion can approximate external, arousal-modifying events. Data show that enhanced locomotor activity, hence enhanced arousal, following treatment with amphetamine does not alter the intensity of sexual approach behavior in male or female rats (Ågmo, 2003a; Ellingsen and Ågmo, 2004). The dopamine antagonist

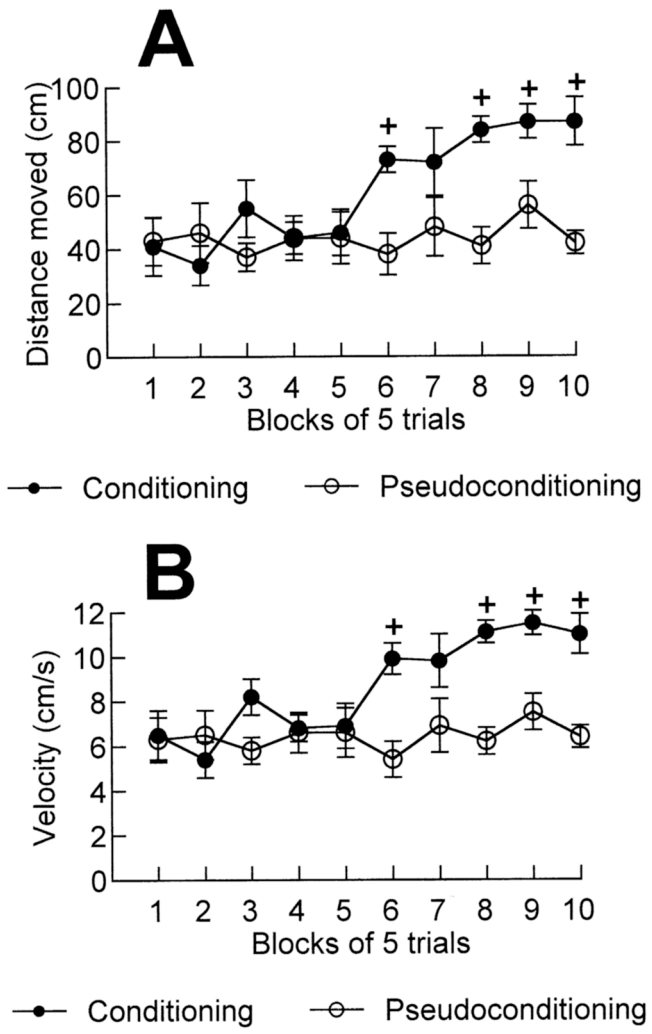


Fig. 2. Increase in general arousal, expressed as increased distance moved and enhanced velocity of movement, during acquisition of a sexual approach response. Mean ± SEM of (A) distance moved and (B) mean velocity of movement while moving during a 10-s presentation of an initially neutral olfactory stimulus in a group of rats (N = 8, Conditioning) in which the stimulus preceded the introduction of a sexually receptive female and in a group of rats (N = 8, Pseudoconditioning) in which the stimulus was presented independently of the introduction of the female. Each data point is the mean of 5 trials. Each trial ended when the male had performed one intromission. In the Conditioning group, the distance moved as well as the velocity of movement increased gradually as training progressed, while no such effect was present in the Pseudoconditioning group. This shows that the association of the stimulus with the execution of a copulatory response (intromission) enhanced arousal. The simple exposure to the stimulus in a context where copulation occurred independently of it failed to affect the arousal response. The lack of a significant group difference at block 7 may be attributed to the unusually large standard error at that block. We ignore the reason for this. Statistical evaluation of the data shown here were made with the Mann-Whitney U-test. The groups were compared at each of the 10 blocks, and the obtained p-value was adjusted according to Conover (1999). For further details of this experiment see Kvitvik et al. (2010). +, different from pseudoconditioning, $p < 0.05$.
Modified from Kvitvik et al. (2010). Reproduced with permission from Elsevier.

flupenthixol also failed to modify approach behavior in doses that strongly reduced locomotor activity in both sexes. Another study confirmed the lack of stimulatory effect of amphetamine on female rat sexual approach behavior (Guarraci and Clark, 2003). Non-dopaminergic drugs affecting locomotor activity also fail to modify sexual approach in male rats (e.g. Chu and Ågmo, 2016). Doses of the peripheral opioid agonist loperamide that strongly reduce activity leave sexual approach unaffected (Ågmo, 2003a). Taken together, the data mentioned here show that general arousal is essentially unrelated to the intensity of sexual approach behaviors in rats. In fact, it is possible that the rather simple motor activities leading to reduced distance to a sexual incentive are unaffected by arousal level. This would make rodents different from humans, since sexual approach is facilitated by enhanced arousal in the latter species. We believe that there is a simple explanation: Whereas the responses to sexual stimuli are automatic in rodents, humans need to perform a cognitive evaluation of the context before initiating approach behavior. It is well known that cognitive evaluations may be facilitated by increased arousal. For example, a cold stimulus applied to the cheeks not only enhances arousal and activity in the prefrontal cortex, but also improves performance on cognitive tasks such as the Stroop test (Okura and Rikimaru, 2021). Arousal-enhancing pictures affect event related potentials and contingent negative variation recorded during a cue-probe task (Cudo et al., 2018), suggesting improved cognitive control.

5.3. Viscerosomatic responses and general arousal

Visceral responses, mainly genital blood flow, to sexual stimuli have been the subject of much research. It is possible that these responses are associated with enhanced general arousal. This could easily be shown by calculating correlations between the magnitude of the genital response (erection and vaginal lubrication) and typical indicators of general arousal such as blood pressure, heart rate, respiration frequency or the galvanic skin response. Although all these variables have been recorded in the same individuals in many studies (e.g. Suschinsky and Lalumière, 2012), reports of correlations are exceptional. In fact, there is only one study in which correlations between the genital response and heart rate and the galvanic skin response were calculated (Laan et al., 1995). Contrary to what could be expected, both vaginal pulse amplitude and vaginal blood volume during exposure to a pornographic movie segment were unrelated to heart rate and the skin response. This observation suggest that the intensity of genital arousal is not a main determinant of general arousal in women. The possible relationship between the intensity of the viscerosomatic response of erection and the level of general arousal has not been studied.

Whereas the effects of genital responses on general arousal is unclear, there are many observations regarding the inverse relationship, i.e. the effects of general arousal on genital responses. In fact, there is a reasonable amount of data available from studies that have employed objective measures of genital responses to explicit sexual stimuli after manipulations of the level of general arousal. In an elegant experiment by Meston (2000) women were shown a sexual stimulus (pornographic movie segment) either when rested or after intense physical exercise. It is well known that exercise increases general arousal. The vaginal response to the movie segment was enhanced in the women having engaged in physical exercise, i.e. women with enhanced general arousal. Similar effects were found after treatment with ephedrine, an agonist at postsynaptic adrenergic α and β receptors (Meston and Heiman, 1998). Stimulation of these receptors enhances activity in the sympathetic nervous system, another arousal-producing event. Anxiety has also been found to increase the vaginal response to sexual stimuli (Hoon et al., 1977; Palace and Gorzalka, 1990), and anxiety is thought to enhance arousal (Ramsey, 1943). Studies in men have also shown that enhanced general arousal, because of conditioned fear, leads to enhanced penile response to a sexually relevant stimulus (Barlow et al., 1983). Likewise, an emotionally arousing, non-sexual video fragment enhances the penile response to an ensuing pornographic video segment (Wolchik et al., 1980). Since enhanced response to a constant stimulus must be due to increased motivation, it can tentatively be concluded that increasing general arousal stimulates the activity of the sexual central motive state, hence sexual motivation, in men and women.

Although there are many studies supporting the conclusion above, it must be mentioned that an extensive review of the effects of anxiety on

sexual responses found that the relationship may be more complicated (e.g. Bradford and Meston, 2006). Several studies have failed to find any effect at all of anxiety on genital responses (e.g. Elliott and O'Donohue, 1997; Sipski et al., 2004) while others have reported decreased response (Masters and Johnson, 1970). Consequently, it is premature to make any firm affirmation concerning the influence of general arousal on genital responses in men and women.

Pupil dilation is a non-sexual response to many kinds of stimuli (reviewed in Einhäuser, 2017). When recorded during exposure to a sexual stimulus, it might be considered a visceral response to this stimulus. If young men and women are stressed and concurrently exposed to pictures with erotic content, the pupil dilation are larger than in the absence of stress, and the stress effect is larger for erotic pictures than for neutral pictures (Finke et al., 2018). The stress-induction procedure was found to increase blood pressure and heart rate, showing that general arousal indeed was enhanced. This study suggests that general arousal not only enhances sexual visceral responses to sexual stimuli, but also non-sexual visceral responses to such stimuli. We propose that this action is mediated by the sexual central motive state, and that the heightened pupillary response is indicative of facilitated cognitive processing of sexual stimuli.

The role of general arousal for the viscerosomatic responses in rodents is poorly known. Only one study has evaluated the consequences of enhanced general arousal for penile erection. Rats were subjected to an anxiety-inducing procedure, and erections stimulated by apomorphine were quantified. The anxiety procedure enhanced heart rate and mean arterial pressure, confirming increased arousal. The number of erections observed in these animals was reduced compared to controls (Brien et al., 2002). Even if these data are not conclusive, they suggest that there might be a negative relationship between increased general arousal and erection. Nevertheless, it is probably prudent to abstain from any conclusion until more data have become available.

A curious illustration of a possible relationship between general arousal and sexual responses is found in the association between yawning and penile erection in male rats. Prolonged observation has revealed that erection and yawning often coincides (Holmgren et al., 1985). A major function of yawning is to enhance general arousal in environments providing little stimulation (Baenninger, 1997), such as a rat's home cage. The momentarily enhanced arousal leads to a genital response, suggesting activation of the central motive state. Whether the association between yawning and sexual activation also is present in humans is not known. Regardless of this, there are probably other, equally likely, explanations for the temporal coincidence of yawning and erection.

We know of no data concerning vaginal responses and general arousal in rodents. In the absence of more experimental evidence in favor of effects of general arousal on genital responses in males and females we propose that rats are different from humans in the way that variations in general arousal have variable effects on genital responses to sexual incentives.

There is an indirect way in which general arousal could affect human genital responses. The level of arousal is known to be a determinant of the efficiency of cognitive processing, in the way that moderate arousal facilitates processing whereas very low or very high arousal have deleterious effects (e.g. Lambourne and Tomporowski, 2010). The importance of cognitive processes for genital responses in men and women has been well established (Tavares et al., 2020). Interference with cognitive processing of sexual stimuli leads to reduced genital response. For example, while women were watching a pornographic movie, they were asked to perform tasks of increasing difficulty. The lowest level of difficulty was no task, and the highest level was a requirement to classify pairs of digits according to complex rules, and verbalize the result aloud (Salemink and van Lankveld, 2006). The classification rules were complex indeed: together the digits form a number; odd numbers under 50 are classified as A; even numbers under 50 are classified as B; odd numbers over 50 are classified as B; even numbers over 50 are classified as A (Salemink and van Lankveld, 2006, p. 182). The more difficult the task, the larger the reduction of the genital response. Similar data have been reported from a male sample (van Lankveld and van den Hout, 2004). Manipulations facilitating attention to sexual stimuli enhanced responses in men and women (Both et al., 2011; Farkas et al., 1979). Perhaps the somewhat variable effects of arousal-enhancing procedures on human genital responses can be explained by their unintended, equally variable, effects on cognitive processing.

5.4. Transition from approach to copulation

In humans, the transition involves a conscious decision about whether to proceed with sexual activities or not to proceed. Decision-making is known to enhance general arousal (Johnson, 1963) as manifested in increased heart rate and galvanic skin response. Likewise, pupil dilation, an exquisite indicator of general arousal (Bradley et al., 2008) occurs during the decision process (de Gee et al., 2014 and references therein). It seems likely that the decision to pass from sexual approach behaviors to sexual activity leads to enhanced general arousal as other decisions do. The same should be the case for the contrary decision, not to proceed with sex. Even though the cognitive processes underlying the decision to engage in sexual activities are poorly known, some informed speculation is possible.

It seems that most humans will not initiate partnered sex without explicit or implicit consent from the partner. In fact, in Western societies, and probably in many others, sexual approaches and ensuing sexual activities are socially acceptable only between consenting individuals. Predictions about obtaining consent for sexual interaction are probably an important part of the initial transition from approach to further sexual activity. However important such predictions may be at early stages of sexual approach, these predictions must be confirmed before manifest sexual activities start. Thus, the approaching individual needs to determine whether the approached individual is consenting to sexual activity or not. There seems to have existed conflicting views on how consent or lack thereof is communicated to a potential partner. It now appears that the consenting individual uses direct or indirect verbal expressions as well as direct and indirect non-verbal cues to communicate consent (reviewed in Fenner, 2017). These strategies are also used in pornographic movies (Willis et al., 2020), which may be important since, for many young people, such movies have become the main source of sex education.

Men and women communicate consent in similar ways, and both sexes understand their partner's communication equally well (Hickman and Muehlenhard, 1999), even in casual encounters (Beres, 2010). The fact that men accused of rape or sexual harassment frequently argue that they misunderstood the message from the non-consenting party can be considered a kind of unfounded self-justification (Maruna and Mann, 2006).

Provided consent is obtained, direct physical interaction between the approaching and approached individuals will usually ensue. This will further enhance general arousal (see below). The contrary outcome, the potential partner's refusal of consent, may also lead to enhanced arousal, perhaps because of frustration. Even the act of refusing further interaction may lead to enhanced arousal. There is some indirect evidence for this (Chen et al., 2014; Zhou et al., 2009). Thus, whatever the outcome, the transition process probably enhances general arousal, and consequently contributes to the activity in the central motive state. Possible consequences are that the rejected individual persists in approach behaviors even if the partner has declined, or that these behaviors become directed towards another individual. There is, however, no direct evidence for any of these alternatives. Enhanced arousal in the rejecting individual will probably reinforce some central motive state different from the sexual.

In rodents, the search for consent before initiating copulation does not seem to be of major concern. One reason for this may be that rodents are not sexually attracted to other individuals unless these others show

unequivocal signs of being ready for copulation. We have carefully analyzed the sexual interactions between male and female rats in a seminatural environment, and we have found that sexually experienced males rarely approach a non-receptive female (Chu and Ågmo, 2015a, 2015b; Le Moëne et al., 2020a). An example is shown in Fig. 3. Furthermore, a male almost never mount a female not showing paracopulatory behavior (Bergheim et al., 2015). Thus, the execution of copulatory acts on part of the male depends on the female's behavior. Likewise, males need almost always to pursue the female before they come into position for executing a mount. In anthropomorphic terms we could say that the female rat invites the male to copulate, i.e. she expresses her consent to having sex, and the male can accept or not accept that invitation by pursuing or not pursuing the female. It appears, then, that sexual interactions among rats are limited to consensual sexual activities. This is not true in standard observation procedures, in which the experimenter subjects the rats to forced sexual interaction, but it is true in ecologically valid procedures, like the seminatural environment. In any case, whereas the transition from approach to copulation in humans is based on a conscious decision, there is no reason to believe that something similar occurs in rats. There, the transition appears to be an automatic process. Thus, there is no arousal-enhancing decision making involved.

The behavior patterns immediately preceding copulatory acts, paracopulatory behavior in females and pursuit of the female in males, are of relatively short duration. Female paracopulatory behavior, preceding 98% of male mounts, lasts only 2 s, and male pursuit, preceding 84% of mounts, lasts 1.96 s (Bergheim et al., 2015). However, both male pursuit of the female and female paracopulatory behaviors require intense motor activity, and that activity leads to enhanced heart rate and blood pressure, as mentioned. If we accept that these circulatory responses are indicative of increased level of arousal, we must conclude that the transition to copulatory acts is inevitably associated with increased general arousal in male and female rats.

A role for general arousal in the transition is also suggested by studies showing that increased arousal produced by non-sexual stimuli may facilitate transition in male rats. Tail pinch and electric shocks have an immediate stimulatory effect on copulatory behavior in male rats (Barfield and Sachs, 1968; Leyton and Stewart, 1996). This is also the case for conditioned fear arousal (Crowley et al., 1973). Prior to the tests for copulatory behavior, a tone had become associated with painful electric shock in sexually inactive males. When the tone, without subsequent shock, was presented when a sexually receptive female was available, almost all males mounted within seconds. It is not known if experimental treatments increasing general arousal also enhance female sex behavior, but they do facilitate the display of male behavior patterns in female rats (Crowley and Ward, 1974; Krieger and Barfield, 1976).

In sum, transition from sexual approach to copulation in humans depends on a decision-making process, which enhances general arousal. In rats, transition is accompanied by intense muscular activity, likewise enhancing arousal. Thus, even though the source of increased arousal is different in these two species, a facilitative effect on the initiation of copulation may be common.

5.5. The copulatory act

In humans, copulatory acts are often preceded by tactile stimulation not involving the genitals. Mechanical stimulation of the skin, particularly in the pectoral area in women as well as of both ends of the digestive canal in men and women seem to be efficient stimuli for further enhancement of general arousal and sexual motivation (Nummenmaa et al., 2016). We propose that general arousal is the main contributor to the increase in sexual excitation. Sooner or later, the genitals will also be the receivers of mechanical stimulation. For example, touching the glans clitoris in a repeated, rhythmic motion is highly efficient for enhancing self-reported arousal (Herbenick et al., 2018b). In fact, execution of all kinds of sexual acts leads to further enhancements of general arousal. In the human, there is a substantial increase in sympathetic activity during intercourse, manifested in heightened blood pressure and heart rate, among other things (Cheitlin, 2005; Falk, 2001; Masters and Johnson, 1966). It has been reported that orgasm is associated with a spike in sympathetic outflow, particularly manifested in increased heart rate (e.g. Carmichael et al., 1994; Dubray, 2013; Xue-rui et al., 2008). In women, the increase in heart rate at orgasm is correlated with subjective orgasm intensity (Alzate et al., 1989; Levin and Wagner, 1985). We have not been able to find any data from men about the relationship between the intensity of autonomic responses and the intensity of orgasm.

We propose that the augmented general arousal will feed back to the

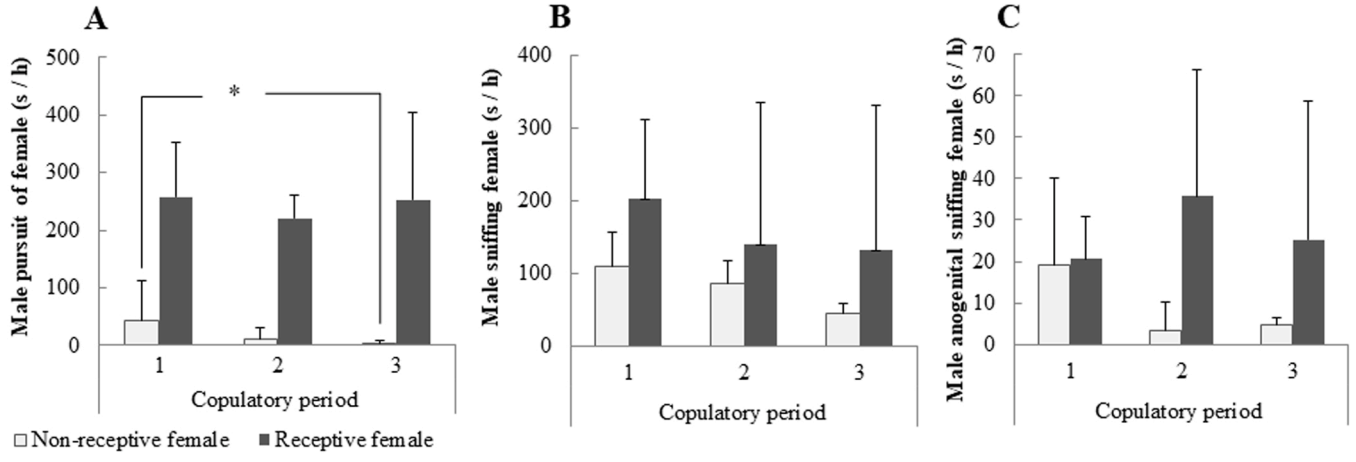


Fig. 3. Male pursuit (a), male sniffing (b), and male anogenital sniffing (c) of receptive and nonreceptive females during the acquisition of sexual experience in a seminatural environment. The first copulatory period was the males' first encounter with a sexually receptive female. A copulatory period is a bout of continuous sexual activity starting with a mount or intromission and continuing until the beginning of a period of sexual inactivity lasting for more than 60 min. Pursuit of nonreceptive females is very low already during the initial sexual encounter, and close to 0 at the third encounter. Pursuit is the behavior immediately preceding mounting. The other social behaviors, sniffing and anogenital sniffing, are not associated with sexual activity. It appears that males rapidly learn to abstain from trying to engage in sexual activity with nonreceptive females. Data are median ± semi interquartile range. Statistical evaluation was made with Friedman's ANOVA. Following significant result, pairwise comparisons were made with the Wilcoxon test. Significance levels were adjusted with the Bonferroni correction. N = 7. * Different between periods, $p < 0.05$, corrected for multiple comparisons.
Reprinted from Chu and Ågmo (2015b). With permission from the American Psychological Association.

sexual central motive state and further enhance responsivity to the stimuli generated by the sexual activity. It is also likely that the sensory stimulation produced by sexual acts will directly feed back to the sexual central motive state, enhancing its activity. The combined effects of general arousal and sensory feedback will eventually elevate the activity of the sexual central motive state to such a level that seminal emission and ejaculation, combined with the subjective experience of orgasm, occur in men. In women, the intensely active sexual central motive state will cause rhythmic contractions of pelvic muscles, similar to those causing emission and ejaculation in men, as well as the experience of orgasm (Bohlen et al., 1982; Cour et al., 2013; Shafik et al., 2009). The fact that women are less likely than men to achieve orgasm during a sexual encounter (e.g. Frederick et al., 2018) may have many explanations, including a need for a higher level of excitation for activating the orgasm response, a slower increase in excitation than men, or need for greater variation in the location of genital stimulation in women. An analysis of this issue is beyond the purpose of the present communication.

The fact that men may ejaculate spontaneously, i.e. without purposeful genital stimulation, and that women may experience orgasm in many non-sexual contexts does not necessarily contradict the proposal made above. In men, it is supposed that most spontaneous ejaculations (nocturnal emissions) are associated with the experience of orgasm, but there are no direct data on this issue. It seems that ejaculation is presupposed to be synonymous with orgasm, even when it is known that they are separate events (Gerstenberg et al., 1990). In women, orgasms may be activated by stimulation of non-genital body parts or by visual or auditory stimuli (Herbenick et al., 2018a), in addition to mental representations of genital stimulation, as already mentioned. The causes of these ejaculations or orgasms are not well known. In men, many of the orgasm-associated nocturnal ejaculations are accompanied by dreams with sexual content, but they may also occur in the absence of such dreams (Yu and Fu, 2011). Similar data have been reported for nocturnal orgasms in women (Henton, 1976). The physiological reactions associated with ejaculations and orgasms unrelated to genital stimulation are unknown. Nevertheless, these spontaneous events do not invalidate the proposal that orgasm is normally dependent on the synergistic action of general arousal and the sexual central motive state.

The execution of copulatory acts leads to increased blood pressure and heart rate in male and female rats (McBryde et al., 2012; Saito et al., 2001; Terada et al., 2003) in the same way as in humans. In male rats, the increase reaches a maximum at ejaculation (Saito et al., 2001; Terada et al., 2009). Curiously, male ejaculation is associated with a sharp increase in heart rate also in females (Terada et al., 2003). There is, then, reason to believe that general arousal contributes to the activation of the ejaculatory reflex in male rats, and that male ejaculation alters general arousal in the female. Whether the female experience something similar to the human orgasm is, however, an open question, as mentioned.

There are also data showing that arousal-enhancing events completely unrelated to sexual activity may facilitate ejaculation. Conditioned fear in rats reduces the number of intromissions needed for ejaculation (Beach and Fowler, 1959a). A similar effect was observed after treatment with an anxiogenic drug (Fernández-Guasti et al., 1990). Repeated electric shock also reduces the number of pre-ejaculatory intromissions and the ejaculation latency (Caggiula and Vlahoulis, 1974). Thus, increases in general arousal seem to contribute to the level of arousal in the sexual central motive state, facilitating the attainment of the ejaculatory threshold.

In Table 1 we have summarized the effects of altered general arousal on the different stages of sexual interaction in rats and humans. It can be seen that enhanced general arousal has been found to facilitate all elements of human copulatory interactions. In male and female rats, enhanced arousal leaves sexual approach behaviors unaffected, whereas the visceral responses are reduced in males. With these exceptions, general arousal affects sexual motivation in similar ways in rats and humans.

Table 1
The effects of altered general arousal on sexual motivation at each of the stages of sexual interaction in male and female rats and humans. ↑, experimental manipulations further enhancing arousal stimulates the sexual response. ↓, experimental manipulations further enhancing arousal reduces the sexual response. 0, no effects. -, no data available. For supporting references, see text.

Stage of sexual interaction	Effects on sexual motivation			
	Rats		Humans	
	♀	♂	♀	♂
Response to sexual incentives	↑	↑	↑	↑
Sexual approach behavior	0	0	↑	↑
Visceral responses	–	↓	↑	↑
Transition to copulation	↑	↑	↑	↑
Copulation	↑	↑	↑	↑

5.6. Aftereffects of sex

It appears that orgasm in men and women is followed by a period of reduced general arousal. Kinsey et al. (1953) reported that relaxation, quiescence of the body and sleepiness follow orgasm. This notion appears to have support in popular belief. A majority of women and men reported improved sleep after orgasm in an internet-based survey (Lastella et al., 2019). However, the only experimental study of sleep following sexual activity we know of does not confirm this belief. Electroencephalographic recordings from a small number of young men and women showed that orgasm induced by masturbation did not lead to a sleep pattern different from that following masturbation without orgasm or after reading a neutral text (Brissette et al., 1985). Even though sleep patterns are not altered by preceding sexual activity, it is not unreasonable to suggest that orgasm is followed by a period of reduced general arousal in the human. Whether each orgasm is followed by reduced arousal or not in multiorgasmic women is uncertain. Questionnaire data show that women experiencing several orgasms during partnered sex report increased arousal following the first orgasm, whereas women engaged in solitary sex report reduced arousal (Gérard et al., 2021). Unfortunately, the changes in arousal around the orgasm ending an episode of sexual activity in the multiorgasmic women were not determined. In multiorgasmic men, reduced arousal following the last ejaculation in a series has been reported (Griffin-Mathieu et al., 2021).

In rodents, there seems to be a substantial reduction in arousal following sexual activity. Ejaculation in male rodents is immediately followed by a strong reduction in general arousal lasting for several minutes (e.g. Dewsbury, 1967), even in the case when copulation eventually is resumed. One manifestation of this reduced arousal is the fast postejaculatory decline in heart rate in male rats (Terada et al., 2009). Since female rats do not display any particular behavior indicative of orgasm, it is difficult to know if there is any postorgasmic decline in general arousal. Moreover, it is unclear whether females ever experience something similar to orgasm, as mentioned. Regardless of the female subjective experience, the receipt of an ejaculation produces not only withdrawal from the male (Erskine, 1989) but also of reduced ambulatory activity for a short time (Dewsbury, 1967; Krieger et al., 1976).

A few studies in rodents suggest that copulation facilitates sleep. In male rats, prolonged sexual activity enhanced total sleep duration during the two hours following cessation of sexual activity (Boland and Dewsbury, 1971). Copulation until exhaustion or three ejaculations were found to increase slow wave sleep and reduce wakefulness whereas one ejaculation had no effect (Vazquez-Palacios et al., 2002). It appears possible to conclude that prolonged sexual activity actually enhances sleep in rodents. However, the studies mentioned above have been subjected to criticism, and it is not evident that sex alters sleep at all (Meerlo, 2003). The consequences of copulatory activity for sleep in female rats are unknown. Despite the lack of data from females, we propose that the effect, or lack thereof, of sex on sleep in rats are not so

different from those in humans.

Regardless of the potential effects on sleep, the postorgasmic state is characterized by reduced general arousal in both rats and humans. It is also associated with reduced sexual motivation. Whether this reduction is causally related to reduced general arousal is not known. Other factors, like negative alliesthesia, may be far more important.

5.7. General arousal in non-sexual contexts

Sexual activity is not unique in its capacity to enhance general arousal. The simple introduction of a second drinking bottle into the home cage of male rats causes a marked increase in heart rate, arterial blood pressure and plasma corticosterone regardless of whether the bottle contains plain water or a highly palatable sucrose solution (Egan and Ulrich-Lai, 2015). It was suggested that novelty was the main factor causing all these physiological responses, indicative of enhanced arousal. Likewise, reinforcement with food or drink leads to arousal increases (Killeen et al., 1978). It may be concluded that all kinds of events, like novelty, feeding (Campbell and Sheffield, 1953; File and Day, 1972), drinking, sex and physical exercise are able to enhance general arousal.

In the same way as entirely irrelevant, arousing stimuli stimulate the display of sexual behavior (see above), such stimuli facilitate responses to other incentives. Tail pinch or loud noises induce eating in sated rats (Antelman and Szechtman, 1975; Fass et al., 1981; Martin, 1984; Wilson and Cantor, 1986), increases the rate of self-stimulation of the brain (Katz and Roth, 1979; Sadowski et al., 1984), and stimulates consumption of sweet or salty liquids (Marques et al., 1979). All these observations suggest that general arousal contributes to all kinds of central motive states. Such an action of enhanced arousal is entirely in line with the basic property of arousal as an "energy mobilizer" proposed by Duffy (1957) many years ago.

6. Neurobiology of the sexual central motive state

McDougall was uninterested in the physiological events underlying the sexual instinct, probably because the brain sciences and endocrinology were in their infancy at the time he elaborated his theories. They could simply not provide any useful information, according to his judgment. Freud made frequent remarks suggesting that he expected that these disciplines in some distant future would provide explanations for some of the phenomena he observed. At the same time he considered the search for neurobiological explanations outside the scope of psychology. With the enormous advances within the fields now known as endocrinology and neuroscience it has become possible to make some informed speculations concerning the neurobiology of sexual motivation, or more specifically, of the sexual central motive state.

Any analysis of the sexual central motive state needs to take into account that sexual motivation, hence the activity and reactivity of the sexual central motive state, varies over time within the individual. These variations may be slow, manifesting themselves over periods of months or years. An example of slow variations in sexual motivation can be the changes occurring during puberty. The variations may also be fast, manifesting themselves in minutes or even less. An example of fast variations can be found in the response to pornographic movies in men and women. Genital blood flow is increased within one or two minutes of exposure to the movie, and this response is controlled by the sexual central motive state, according to the model used here. In the ideal case, we should also be able to explain why some individuals show a much larger response to sexual stimuli than others. Stable interindividual differences in responsiveness to sexual stimuli have been described both in humans (Diamond et al., 2017; Hill and Preston, 1996) and rats (Pattij et al., 2005; Snoeren et al., 2011). These differences must be attributed to differences in the activity of the sexual central motive state. Consequently, any description of the neurobiological bases of the sexual central motive state needs to answer at least three questions. One concerns the neurobiological bases of the long-term responsiveness or basic activity, another concerns the short-term regulation of the sexual central motive state, and the third concerns the causes of the interindividual variation. If general arousal indeed contributes to the sexual central motive state, then arousal must modify one or several of the factors controlling the momentaneous activity of that state. General arousal can be expected to act fast, and is probably of minor importance for the long-term regulation. It is, consequently, unlikely that general arousal is a major determinant of the interindividual differences in basic activity or responsiveness of the sexual central motive state.

6.1. Gonadal hormones

6.1.1. Males

In male rats, abundant evidence has established that gonadal hormones are needed for the long-term regulation of the responsiveness to sexual stimuli (reviewed in Hull and Rodríguez-Manzo, 2017). To be more exact, androgens acting on the androgen receptor, and estrogens acting on the estrogen receptor α, are needed for the complete expression of male rat sexual approach as well as copulatory behavior (e.g. Attila et al., 2010; Ogawa et al., 1997; Sano et al., 2013). It must be remembered that the necessary estrogens are produced locally in the brain through aromatization of testosterone. In men, there are many observations suggesting that actions on estrogen receptors are not needed, and that androgens acting on the androgen receptor are the sole responsible for maintaining the activity of the sexual central motive state (see Le Moëne and Ågmo, 2019 for a review). Thus, in rats and humans there is no doubt that testicular hormones, either directly or via aromatization, are in charge of the control of the long-term activity of the sexual central motive state. The molecular mechanisms of action of these hormones remain obscure.

In castrated male rats, neither showing sexual approach nor copulatory behavior, testosterone treatment starts to have effects after several days and behavior is not completely restored until after 15–20 days of treatment (e.g. Ågmo, 2003b; Attila et al., 2010). Likewise, sexual behaviors persist for several days after castration, even though blood concentration of testosterone is below detection limit at about 6 h postcastration (Kashiwagi et al., 2005). Since testosterone is a transcription factor, such slow actions can be expected (Davey and Grossmann, 2016). These facts suggest that it is unlikely that this androgen is involved in the short-term fluctuations in activity of the sexual central motive state.

In addition to the genomic actions of testosterone just mentioned, relatively rapid actions of this steroid have been described in several systems (Michels and Hoppe, 2008). Some of these actions may be attributed to transcription activated by the nuclear androgen receptor (Heinlein and Chang, 2002), but membrane bound androgen receptors have also been described (Thomas, 2019). This means that short-term effects of testosterone cannot be excluded despite the overwhelming evidence that androgen actions on male sexual behavior are slow and long lasting.

The blood concentration of androgens in adult men and male rats is far above that needed for maintaining sexual functions. Only severe hypogonadism or castration brings androgen concentration below the threshold needed for maintaining sexual behavior, which means that the sexual central motive state no longer respond to sexual stimuli (Beach and Holz-Tucker, 1949; Bremer, 1958; Steinach, 1910). Whenever total testosterone concentration in men is below 8 nmol/l, hypogonadism is diagnosed, and sexual functions are compromised (Kwan et al., 1983; Wu et al., 2010). The healthy range is considered to be from 9 to 32 nmol/l (Arver and Lehtihet, 2009), and the mean concentration of testosterone in healthy men between 19 and 40 years was found to be 25.11 nmol/l in a British sample (Bhasin et al., 2011). Thus, only drastic reductions in circulating testosterone are associated with impaired sexual function.

In healthy men and intact male rats there is no correlation between

blood androgen concentration and sexual activity (Brown et al., 1978; Damassa et al., 1977; van Anders, 2012). This appears to be true for all male mammals studied so far (von Holst, 1989). Administration of supplementary androgens will not enhance sexual motivation, neither in men nor in male rats (Anderson et al., 1992; Bagatell et al., 1994; Buena et al., 1993; Conaglen and Conaglen, 2009; Damassa et al., 1977; Yates et al., 1999). To the contrary, sexual functions are improved by treatments enhancing testosterone concentration in hypogonadal men (for a review, see Ponce et al., 2018). The fact that physiological testosterone concentration is far above the level needed for maximal basic activity in the sexual central motive state makes it unlikely that even large intra-individual variations in testosterone availability are associated with variations in sexual motivation. Moreover, the lack of correlation between testosterone levels and individual sexual performance makes it unlikely that interindividual differences in the latter can be explained by the former.

Data support the hypothesis that intraindividual variations in sexual activity are not testosterone-dependent, at least not in rats. Testosterone secretion fluctuates, and in rats, there is a tenfold difference between peak and nadir blood concentration during the light/dark cycle (Södersten et al., 1980). There is no corresponding variation neither in the intensity of copulatory behavior nor in sexual approach behaviors (Bakker et al., 1995). All these data show that short- or long-term variations in blood androgen concentrations do not modify sexual behavioral functions provided that the concentration is above threshold.

Results from studies in rats, guinea pigs and rabbits show that differences in testosterone levels cannot explain the individual differences in the responsivity to sexual stimuli. We postulate that this responsivity is determined by the basic activity in the sexual central motive state, and that both are manifested in the ease of activation of sexual approach and copulatory behavior. If, for example, all individuals in a group of castrated rats were treated with a fixed dose of testosterone, and if the individual differences in precastrational sexual performance were replicated, then it could be concluded that individual variation in testosterone availability are unrelated to variations in the responsivity to sexual stimuli. This has been shown to be the case (Beach and Fowler, 1959b). Similar studies in guinea pigs (Grunt and Young, 1952) and rabbits (Ågmo, 1976) provided identical results. Unfortunately, no comparable data from men are available, but there is no particular reason for believing that men should be different from rats in this respect.

In male rats, exposure to sexual incentives and copulation increase the blood concentration of androgens (Amstislavskaya and Popova, 2004; Bonilla-Jaime et al., 2006; Graham and Desjardins, 1980; Kamel and Frankel, 1978; Kamel et al., 1975, 1977; Oaknin et al., 1989). Similar data are available from mice, hamsters, bulls, rams and rabbits (reviewed in Nyby, 2008), In men, exposure to sexual stimuli does not alter blood concentration of testosterone (e.g. Carani et al., 1990; Krüger et al., 1998; Lee et al., 1974; Lincoln, 1974; Rowland et al., 1987; Stearns et al., 1973), whereas many studies have found elevated concentration in saliva (e.g. Hellhammer et al., 1985; Roney et al., 2007, reviewed in Roney and Gettler, 2015). Some have gone so far as to report that testosterone is released in response to odor from women close to ovulation but not from women in the luteal phase (Miller and Maner, 2010), an observation that could not be replicated (Roney and Simmons, 2012).

The significance of salivary testosterone is not immediately apparent. It can be assumed that determinations of steroids in saliva have become commonplace mostly because of the ease of obtaining samples. However, there are some difference, and at least one could be of importance. Since there usually is an equilibrium between circulating androgen concentration and concentration in target tissues, the former have physiological significance. Saliva is excreted outside the body, and androgens contained therein have no known function. Thus, variations in saliva concentration are non-consequential unless it is assumed that they coincide with variations in blood concentration. We will not discuss this issue here, but we want to mention that the use of blood rather than saliva samples is a far more direct way to quantify endocrine responses to events of all kinds. Considering this argument, we maintain that the question of whether men respond to sexually relevant stimuli with enhanced androgen release is still lacking a definitive answer.

We mentioned that the effects of testosterone on sexual behaviors are slow. Then, an appropriate question is whether any release in response to sexually relevant stimuli could have any functional significance. There is indeed some evidence suggesting that this may be the case. In rats and mice, reliably responding with testosterone release when exposed to sexual stimuli, there are a few reports showing that such release actually may facilitate some aspects of copulatory behavior. Intravenous injection of testosterone 60 min before a test causes reduced latency to ejaculation and reduced postejaculatory interval (Malmnäs, 1977). Furthermore, ten min preexposure of male rats to an inaccessible, sexually receptive female, leads to reduced mount, intromission and ejaculation latency in an ensuing test with another female (de Jonge et al., 1992). Exposure to an inaccessible female causes testosterone release within minutes (e.g. Kamel et al., 1975; Purvis and Haynes, 1974). The Malmnäs (1977) and de Jonge et al. (1992) studies show that testosterone indeed can have almost immediate effects on copulatory behavior. Similar observations have been made in mice. The mount latency is reduced 60 min after subcutaneous testosterone injection (James and Nyby, 2002). Although suggestive, these scattered studies are not enough for firm conclusions.

It has been proposed that the rapid actions of testosterone on male copulatory behavior may require aromatization to estradiol (Charlier et al., 2015; Cornil et al., 2006). This assertion is supported by an experiment in male C57/Bl6 mice, in which aromatase inhibitors strongly reduced copulatory behavior within 10 min of administration (Taziaux et al., 2007). Until this observation has been confirmed and extended to other mouse strains and rats we prefer not to present any conclusion concerning the importance of aromatization for possible rapid effects of testosterone on sexual behavior.

The observations made in the rat and mouse experiments mentioned above appear to contradict the well established lack of relationship between blood androgen concentrations and the intensity of copulatory behavior. However, it is possible that rapid, non-genomic actions of testosterone are superimposed on the slow, genomic actions, and that these rapid actions indeed modulates sexual behavior. Until further evidence for rapid actions of testosterone on copulatory behavior in rodents emerges, it may be safest to consider such actions as possible but far from established. Furthermore, none of the studies of rapid testosterone actions mentioned here included sexual approach behaviors. Whereas testosterone certainly is needed for maintaining activity in the sexual central motive state, it is uncertain whether this androgen is involved in the momentaneous changes occurring in this state.

Although testosterone release in response to sexual stimuli in men is far from being established, there is an extensive literature about the consequences of such release. Despite extravagant speculations (reviewed in Geniole and Carre, 2018), popular among sociobiologists, about testosterone effects on risk-taking, competitiveness, trust, and some more outlandish situations, the acute effects of testosterone administration on sexual functions have not been evaluated in men. As an approximation, men were allowed to choose between a feminized and a masculinized female face after treatment with a testosterone containing gel. The choice occurred in two contexts, short term and long term mating. A small but significant testosterone effect was seen on the choice of face in the context of long-term mating (Bird et al., 2016). When exercise was used to stimulate testosterone release, there was no effect on mating preferences (Thomas et al., 2021). Whether these data have any relevance whatsoever for sexual functions or not is an open question. Furthermore, considering the low replicability of this kind of studies (Carré and Robinson, 2020) it is perhaps not worthwhile to elaborate on the issue.

Above we have presented data showing that testosterone is necessary

for sexual motivation in men and male rats. However, once testosterone concentration is above a threshold situated far below physiological blood concentrations, there is no relationship between the amount of testosterone available and the level of sexual motivation. Whereas testosterone has a permissive action, it does not seem to be the cause of the interindividual variation in sexual motivation. Any role of testosterone in the short-term regulation, i.e. the intraindividual variation, of the activity in the sexual central motive state in males remains at the level of an interesting hypothesis.

6.1.2. Females

Men and male rats have a relatively constant production of androgens from puberty until death, with only a moderate decline with increasing age (Harman et al., 2001; Kaler and Neaves, 1981; Wang et al., 1993). To the contrary, women and females of most other mammalian species have drastic variations in the production of ovarian hormones within each cycle. The drastic variations in female rodent behavior during the estrous cycle have been well known for at least 100 years, and the dependence of these changes on estrogens have been established beyond doubt. This subject is extensively treated in all textbooks of behavioral endocrinology, and will not be discussed here. We only affirm that the basic activity of the sexual central motive state is dependent on estrogens. Whether stable interindividual differences in estrogen production can explain differences in the intensity of responses to sexual stimuli and sexual behavior is unknown. Females have attracted far less attention than males, and we know of no data concerning the relationship between blood concentration of ovarian hormones during sexual receptivity and the intensity of sexual behavior in cycling females. In ovariectomized rats, the intensity of sexual behavior depends on the amount of estradiol administered until a plateau is reached. Further increases in estradiol dose does not enhance sexual behavior (e.g. Erskine, 1985). The blood estradiol concentration found in cycling females is above the concentration required for maximal response in ovariectomized females (Pfaff et al., 2006). This could indicate that interindividual differences in the availability of estradiol is not the determinant of differences in sexual behavior in females. Perhaps female rodents are similar to males in the sense that once hormone concentration is above a threshold, there is no relationship between that concentration and the intensity of sexual behavior. Nevertheless, it can be concluded that variation in estradiol production and release determines the short-term variation in the activity of the sexual central motive state, such as that occurring during the estrous cycle. Whether estradiol also is important for the momentaneous activity in that state, for example the enhanced activity caused be sexual incentives, is not known.

In distinction to rats, women display sexual activity throughout the menstrual cycle. An enormous effort has been invested in the search for variations in sexual activity and reactivity to sexual stimuli in women during this cycle. Such variation could possibly be attributed to variation in the availability of the different ovarian hormones. However, data are contradictory (reviewed in Kiesner et al., 2020; Wood et al., 2014, see also Meuwissen and Over, 1992; Schreiner-Engel et al., 1981; Stern et al., 2020) and the most reasonable conclusion is that ovarian hormones are not a main determinant of sexual activities in women. This proposal is reinforced by the lack of clear effects of menopause (Kinsey et al., 1953; Laan and van Lunsen, 1997). In sum, it appears that neither the inter- nor the intraindividual variations in the activity of the sexual central motive state is determined by ovarian hormones in women.

Even though it may be unlikely that estrogens are important for the long-term as well as short-term regulation of the sexual central motive state in women, they could have some influence on the momentaneous activity of that state. For example, possible estrogen release in response to sexually relevant stimuli or during sexual activity could contribute to the heightened activity of the sexual central motive state caused by such stimuli or activity. Likewise, potential estrogen actions on general arousal could indirectly affect the sexual central motive state. Since these proposals presuppose estrogen release in sexual contexts, it is important to determine if sexual incentives or sexual activity indeed enhance estrogen release. The very few studies that have quantified estradiol concentrations during sex have been conducted in young women. Neither the exposure to a pornographic movie nor masturbation to orgasm affected blood estradiol concentrations in these women (Exton et al., 1999). Likewise, exposure to a pornographic video segment failed to affect saliva concentration of estradiol (van Anders et al., 2009). An elegant study determined saliva concentrations of estradiol in women attending a sex club in Las Vegas. A baseline sample was compared to a sample obtained from women having observed sexual activity, had been engaged in cunnilingus or fellatio or performed penile-vaginal intercourse. None of these activities had any systematic effect on estradiol concentration (Garcia et al., 2015). More recent data, again based on salivary estradiol, show a clear increase in concentration after exposure to a pornographic movie segment (Shirazi et al., 2018). It is difficult to explain these contradictory observations, but the majority of available data indicate that estradiol is not released during exposure to sexual incentives or during the execution of sexual behaviors. Supposing this to be true, estradiol cannot contribute to the enhanced activity in the sexual central motive state caused by sexual incentives and sexual activities, neither directly nor indirectly through effects on general arousal.

The ovaries release a small amount of testosterone in addition to estrogens and progesterone. The ovarian testosterone release varies according to the menstrual cycle, with a peak around ovulation (Bui et al., 2013). During the follicular and luteal phase, the adrenal cortex releases about as much androgens as the ovaries (Abraham, 1974). Around ovulation, the adrenal contribution is less because of the increased release from the ovaries. There is no cyclic variation in adrenal androgen release, since adrenocorticotropic hormone (ACTH) instead of luteinizing hormone (LH) controls it. It may be important to point out that the major androgens secreted by the adrenal cortex are dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione (Antoniou-Tsigkos et al., 2019). These steroids do not bind to androgen receptors, but are metabolized into testosterone in peripheral tissue (Longcope, 1986; Turcu et al., 2014). This means that there is a delay between release from the adrenals and actions on androgen receptors.

The small effects of menopause, either natural or surgical, has led researchers to look for a role for non-ovarian hormones in women's sexual functions. An old study (Waxenberg et al., 1959) showing that adrenalectomy had deleterious effects on sexual behavior whereas oophorectomy had not pointed in the direction of adrenal androgens as of importance. This has been constantly discussed for the last 60 years, but it now appears that androgens indeed exert a powerful influence on sex in women.

Like in men, there is no systematic correlation between blood androgen concentration and sexual activity in women. A few studies have found a relationship between blood testosterone concentrations and several self-reported aspects of sexual function (Morris et al., 1987; Persky et al., 1982). Others have found no or negative correlations (Bancroft et al., 1983, 1991; Hutchinson, 1995; Yoldemir et al., 2020). In an unusually well controlled study the subjective as well as vaginal response to sexually explicit audiotapes were recorded during different phases of the menstrual cycle in healthy young women, and correlations between these responses and plasma concentrations of testosterone and of the ovarian hormones were calculated (Schreiner-Engel et al., 1981). There was no significant correlation between hormone levels and subjective or vaginal responses.

Although the relationship between testosterone levels and sexual behavior is questionable at best in healthy women, it is generally accepted that severely reduced testosterone availability is associated with sexual dysfunction (Kaplan and Owett, 1993; Mathur and Braunstein, 2010). In women with androgen insufficiency, testosterone treatment restores sexual functions (Bolour and Braunstein, 2005; Islam et al., 2019). As a curiosity, it may be mentioned that the timing of first

coitus in adolescent girls is related to increases in blood testosterone concentration (Halpern et al., 1997). It appears that men and women are quite similar in the way that androgens are needed for normal sexual function, but whenever the androgen level is above a threshold, there is no relationship between androgen availability and sexual motivation, i.e. activity in the sexual central motive state. As we did for men, we propose that androgens are needed for the basic, long-term activity of the sexual central motive state in women. It is unlikely that short-term variations are dependent on androgens.

It is not known whether sexually relevant stimuli cause testosterone release in women. When saliva samples were obtained before and after intercourse in the participants' home, enhanced postcoital saliva concentration of testosterone were found (Dabbs and Mohammed, 1992). Another home based study showed that a period of cuddling with the partner caused an increase in salivary testosterone. Intercourse caused a smaller increase (van Anders et al., 2007). In a controlled laboratory study, a pornographic movie followed by masturbation to orgasm caused an increase in plasma testosterone concentration of borderline significance ($F_{5,45} = 2.34$, $p = 0.0568$; Exton et al., 1999). Women attending a sex club in Las Vegas increased salivary testosterone from a test before entering the club to a test performed immediately after having visited the club and engaged in different sexual activities (Garcia et al., 2015). However, another study failed to find any effect of intercourse on plasma testosterone concentration (Lee et al., 1974). As is the case in men, no possible conclusion about coitus-induced testosterone release in women is possible.

The effects of sexually relevant stimuli in the absence of coitus on blood testosterone concentration has also been studied in young women. Saliva concentration of testosterone was unaffected by an 8 min pornographic movie, and there was no correlation between testosterone concentration and magnitude of the vaginal response (van Anders et al., 2009). Lack of effect of sexually relevant stimuli in women was found in other studies (Goldey and van Anders, 2016; Hamilton et al., 2008a), even when serum testosterone was assayed (Heiman et al., 1991) or when the stimulus was mental representation of sexual activity (Goldey and van Anders, 2011). A more recent study found enhanced salivary testosterone after exposure to a pornographic movie segment, the effect being larger in women tested in the follicular phase (Shirazi et al., 2018). As was the case concerning the effects of intercourse on testosterone release in women, no conclusion is possible concerning the effects of sexually relevant stimuli.

Although it is far from established that sexual stimuli or copulatory activities releases testosterone in women, the acute effects of testosterone administration on sexual functions have been subject of a few studies. In one, testosterone was administered in the form of a sublingual tablet to young women (Tuiten et al., 2000, see also Tuiten et al., 2002). This caused a rapid rise in plasma testosterone concentration. After 90 min, testosterone level was back to baseline. The vaginal response to a pornographic movie increased between 3 and 4.5 h after testosterone administration, i.e. long after that plasma testosterone concentration had returned to baseline. Methyltestosterone was also found to enhance the vaginal response to pornographic movies 4.5 h after administration (Heard-Davison et al., 2007), confirming the long delay between steroid administration and effect. The participants in this study were women in menopause. Thus, the response to testosterone administration is similar in cycling and menopausal women. Vaginal application of testosterone-containing cream, leading to a large increase in serum testosterone (total and free) concentration failed to affect the vaginal response to a pornographic movie at tests performed 4 and 8 h after application (Apperloo et al., 2006). Likewise, oral administration of dehydroepiandrosterone failed to alter the vaginal response to a pornographic movie at a test 45 min postadministration (Meston and Heiman, 2002).

The ensemble of the data reviewed above does not support the notion that testosterone availability is of any major importance for determining the intraindividual variation in activity in the sexual central motive state. First, it is unsure whether blood testosterone concentration will change when the individual is exposed to sexually relevant stimuli or performing sexual activities. Second, even if testosterone would be released, it is unclear whether such release would have any consequence.

6.1.3. Testosterone and general arousal

Although it is unlikely that testosterone is released in men and women by sexual incentives or during sexual activity, such release is firmly established in male rodents. However, it is unclear whether testosterone itself has any significant effect on rodent general arousal, despite the classic studies showing that castration reduces running wheel activity in male rats (Hoskins, 1925) and mice (Daan et al., 1975). Testosterone treatment returns this activity to precastrational levels, an action that is not blocked by the androgen receptor antagonist cyproterone (Stern and Murphy, 1971). The involvement of estrogens in testosterone effects in the running-wheel has been established (e.g. Roy and Wade, 1975), but the role of aromatization is still far from resolved (reviewed in Jardi et al., 2018a). Male mice lacking the androgen receptor showed reduced activity both in the running wheel and in the home cage, suggesting that the androgen receptor indeed is of importance. Castration did not produce any further reduction, but testosterone treatment had a strong stimulatory effect (Jardí et al., 2018b). The non-aromatizable androgen dihydrotestosterone was ineffective, not surprisingly since this steroid has no receptor to act on in these knockouts. However, dihydrotestosterone is inactive also in rats with intact androgen receptors (Roy and Wade, 1975). We have several times manifested that enhanced locomotor activity is a sign of enhanced general arousal, and consequently we must conclude that testosterone indeed has an enhancing effect. If this effect depends on aromatization or not is irrelevant for this conclusion.

A few years ago, we decided to evaluate the putative arousal-enhancing effects of testosterone in a procedure especially designed for assessing arousal level, first described in Arrieta-Cruz et al. (2007). Mice were individually housed in an acrylic cage with sensors detecting horizontal and vertical movements. Activity was continuously recorded, both when the mouse was undisturbed and after presentation of tactile, vestibular or olfactory stimuli. The quantification of responses to these different kinds of stimuli, in addition to determining baseline activity, assured that even small effects on arousal could be detected. It was found that testosterone had only non-significant, marginal effects regardless of whether the steroid was administered in a fast-acting, water soluble preparation or in a slow-acting Silastic capsule (Chu et al., 2015). This study suggests that neither non-genomic nor genomic actions of testosterone have any observable effect on general arousal, at least not in male mice.

We also evaluated the effects of castration of male rats on their locomotor response to a sexual and a social incentive in the procedure illustrated in Fig. 4. Indices of activity were quantified in a small area adjacent to the sexual incentive and in a similar area adjacent to the social incentive. The only differences between intact and castrated males we found were that the castrated males moved a shorter distance in the social incentive area and that these males moved faster in the sexual incentive area (Fig. 5). These minor differences certainly suggest that the absence of testicular hormones has only marginal effects on general arousal. However, all indices of locomotor activity differed between the sexual and social incentives in the intact males, whereas the castrated males responded equally to both incentives. This careful analysis of arousal responses to a sexual and a social incentive show that testicular hormones specifically affect arousal responses to a sexual stimulus. In Fig. 6 we show that the testicular hormones have a specific effect on approach to a sexual stimulus. It can be noted that approach to the social stimulus is not at all modified by castration.

The observations described in the preceding paragraph seem to contradict the data from the running wheel. We will not speculate about the differences between the mechanisms regulating different kinds of

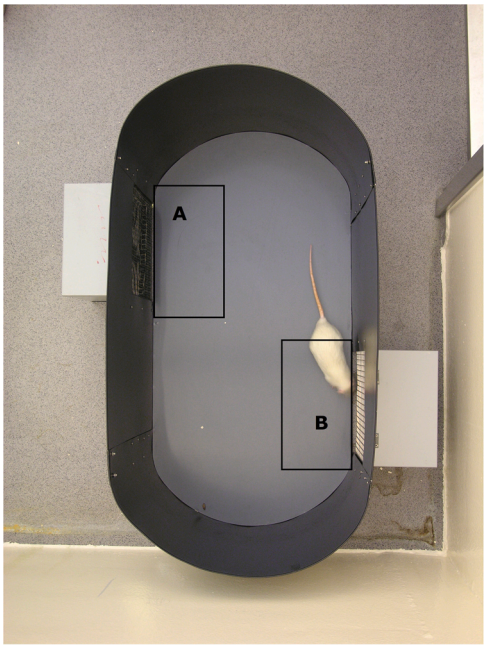


Fig. 4. Arena for the evaluation of sexual incentive motivation in rats. The cages fixed to the outside of the arena contain the incentives, normally one sexual and one social incentive. If the experimental subject is a male, then the sexual incentive is a receptive female and the social incentive may be another male or an ovariectomized female. If the subject is a female, then the sexual incentive is an intact, sexually active male, and the social incentive may be another female (receptive or nonreceptive) or a castrated male. The rectangle on the arena floor outside each incentive animal cage is the incentive zone. The time spent in these zones and the number of visits to them are used to quantify the intensity of sexual motivation. Ambulatory activity, expressed as distance moved, speed of movement or the time spent moving can be determined for each incentive zone or for the entire arena. For further details, see Ågmo (2003a,b) and Ågmo et al. (2004).

locomotor activity. Suffice to say that wheel running may be an artifact of the captive environment, not analogous to any naturally occurring behavior (Sherwin, 1998). Furthermore, low correlations between the many procedures used for quantifying activity have been reported during decades (e.g. Strong, 1957; Tapp et al., 1968; Teske et al., 2014). Based on this short discussion of the effects of testosterone on general arousal, we consider it prudent to propose that such effects are small, if there is any effect at all.

The increased arousal observed in male rats when exposed to sexual incentives and when copulating is apparently unrelated to the enhanced release of testosterone in these situations. Since testosterone release during exposure to sexual incentives and during copulation has not been established, neither in men nor in women, testosterone cannot be involved in the heightened arousal caused by these events.

6.1.4. Estrogens and general arousal

There is an abundant literature showing that estradiol enhances general arousal, either expressed as increased running wheel activity (e.g. Wade and Zucker, 1970), activity in the home cage (e.g. Morgan and Pfaff, 2001) and heightened fear responses in some contexts (e.g. Morgan et al., 2004). In the testing environment shown in Fig. 4, we have determined the effect of different doses of estradiol on parameters of ambulatory activity in ovariectomized females. There was a dose-dependent increase in the time spent moving and in the distance moved in the zone adjacent to the sexual incentive, but no such increase in the zone adjacent to the social incentive (Fig. 7). These data show that estradiol specifically affects arousal responses to sexually relevant stimuli, while not altering the response to other kinds of stimuli. We came to a similar conclusion with regard to androgen actions in the male. However, there are also many failures to find any effect at all of estradiol on locomotor activity and on responses to sudden, unexpected stimuli (e.g. Chu et al., 2015; Le Moëne and Ågmo, 2018a; Le Moëne et al., 2020b). The fact that the actions of estradiol on general arousal are complex and somewhat ambiguous is not of major concern in the present context. Since there is no clear evidence for estradiol release during sexual activities, it is unlikely that this steroid is involved in the enhanced arousal caused by sexual activities or in the momentaneous regulation of the activity in the sexual central motive state. We have already proposed that estradiol does not contribute to the long-term regulation of the activity in that state in women.

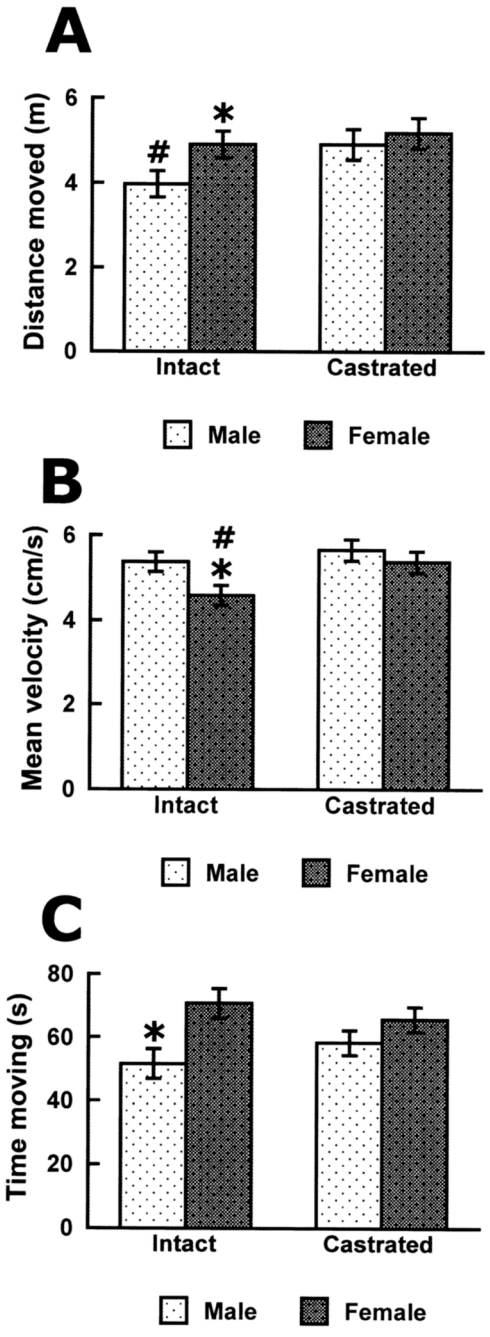
6.2. Non-gonadal steroids released during sexual activity and their effects on general arousal

Sexual activity causes a large release of cortiscosterone in male rats (e.g. Buwalda et al., 2012; Meraz-Medina et al., 2017; Szechtman et al., 1974). In fact, sex was found to cause higher blood concentrations than foot shock and other aversive stimuli in one study (Koolhaas et al., 2011). The simple exposure to a sexually receptive female, without possibility to copulate, is sufficient (Bonilla-Jaime et al., 2006). Concerning females, there is one study showing that serum corticosterone concentration is similar in females tested in paced and non-paced mating procedures, but higher than in control females (Frye et al., 1996). The paced mating procedure allows the female to control sexual interactions, usually by dividing the observation arena with a wall having one or several, small openings. The thin female can move freely through the opening, whereas the bigger male is confined to one part of the arena. Thereby the female can withdraw from the male at any moment, being free to return whenever she likes. In non-paced mating, the female has no escape, and the male is in control of sexual interactions. Females' behavioral and physiological responses to mating differ between these procedures (see, e.g. Paredes and Vázquez, 1999, and references therein). Therefore, it is of some importance that the same magnitude of corticosterone release has been observed after mating in both procedures. We have been unable to find other studies of corticosterone release in response to sexual stimuli or following sexual activity in female rodents. Nevertheless, it is possible that corticosterone release caused by sexual stimuli mediates the increase in activity in the sexual central motive state caused by sexual incentives in rats.

In men, exposure to sexual stimuli in the form of a pornographic movie fails to alter plasma cortisol concentration (Carani et al., 1990; Exton et al., 2000a). In a carefully designed study of the effects of masturbation-induced orgasm in young men, it was found that plasma cortisol was unaltered. However, the men showed all signs of enhanced general arousal, such as increased heart rate, blood pressure and release of noradrenaline (Krüger et al., 1998). Absence of an effect of sexual activity on cortisol release was, in fact, noted already in a famous case study (Ismail et al., 1972). Another study of young men exposed to a pornographic movie revealed a gradual reduction in serum cortisol concentrations as the penis went from a flaccid to a fully erect state (Ückert et al., 2003). Independently of whether this reduction is a reliable phenomenon or not, it may be concluded that there is no increase in cortisol during exposure to sexual stimuli in men. Thus, it appears that such stimuli have completely different effects on glucocorticoid release in male rodents and in men, as also suggested in an extensive review (Alwaal et al., 2015). Women are similar to men in the way that they respond with reduced or unaltered cortisone release to a pornographic movie segment or to masturbation to orgasm (Exton et al., 1999, 2000a; Fuss et al., 2017; Hamilton et al., 2008b; Heiman et al., 1991) regardless of whether cortisone is analyzed in blood or saliva.

Since cortisol is not released during exposure to sexual stimuli or sexual activity in humans it is extremely unlikely that this hormone contributes to the increase in the activity of the sexual central motive state produced by sexual incentives. The fact that acute stress enhances sexual responses as well as cortisol release in men, as mentioned in

Section 6.4, may be interpreted as showing that cortisol indeed enhances activity in men's sexual central motive state. Of course, other consequences of stress could be responsible for this effect. Effects of cortisol on the long-term variation in the activity of the sexual central motive state in men are unclear. In women, chronic stress causes reduced response to a pornographic movie segment concurrent with enhanced saliva cortisol (Hamilton and Meston, 2013). There was no correlation between these two measures, though, making it doubtful whether the increase in cortisol is causally related to the reduced genital response. Adrenalectomy does not reduce sexual activity in male rats, neither in the short- nor in the long-term (Poggioli et al., 1984). Likewise, males treated with substantial doses of corticosterone show unaltered sexual behavior (Retana-Márquez et al., 1998). There are also data showing that chronic stress leaves male rat sexual behavior unaltered, further supporting the notion that corticosteroids do not influence the sexual central motive state (Gorzalka et al., 1998). However, contrary data exist. Several parameters of sexual behavior were found to be slightly but significantly reduced after chronic mild stress (Grønli et al., 2005), while another study showed reduced response to distant sexual incentives in stressed male rats (Hou et al., 2014). Importantly, this effect was associated with impaired testicular function rather than with enhanced corticosteroids. Perhaps this explanation is applicable to other studies reporting reduced sexual behavior after chronic stress. In fact, it has been reported that stress reduces LH and consequently testosterone secretion (Gray et al., 1978), perhaps to such a degree that sexual functions are compromised. Unfortunately, this attractive explanation may be false, since testosterone supplementation does not reduce the inhibitory effects on sexual behavior of some stressors (Retana-Marquez et al., 2003). Nevertheless, the facts that all studied stressors enhance corticosteroids while only some affects male rat sexual behavior (Pednekar et al., 1993; Retana-Marquez et al., 2003) and that chronic treatment with corticosterone is inefficient strongly speak against any role for corticosteroids in the long-term control of male rat sexual motivation.



(caption on next column)

Fig. 5. A–C. Indices of locomotor activity in intact and castrated male rats during simultaneous exposure to a sexual (sexually receptive female) and a social (an intact male) incentive. Activity was recorded in a small area in front of the incentives as illustrated in Fig. 4. Data come from published (Attila et al., 2010) as well as unpublished studies performed in the laboratory. The intact (N = 36) and castrated (N = 35) males were always tested in parallel. Data were analyzed with two-factor ANOVAs with repeated measures on one factor (incentive). Prior to ANOVA, we evaluated the normality of the data distribution with the Shapiro-Wilk test. Homogeneity of error variances in the between-groups factor and the equality of covariance matrices in the within-groups factor were evaluated with Levene's test and Box's M test, respectively. All data reported here satisfied the criteria for parametric ANOVA. Distance moved, main effect of group (intact, castrated), $F_{1,69} = 2.764$, $p = 0.101$, main effect of incentive (male, female), $F_{1,69} = 10.322$, $p = 0.002$, $\eta_p^2 = 0.132$, interaction group x incentive, $F_{1,69} = 1.082$, $p = 0.302$. Mean velocity, main effect of group, $F_{1,69} = 3.847$, $p = 0.054$, main effect of incentive, $F_{1,69} = 4.801$, $p = 0.032$, $\eta_p^2 = 0.065$, interaction group x incentive, $F_{1,69} = 2.716$, $p = 0.104$. Time moving, main effect of group, $F_{1,69} = 0.037$, $p = 0.849$, main effect of incentive, $F_{1,69} = 17.495$, $p < 0.001$, $\eta_p^2 = 0.202$, interaction group x incentive, $F_{1,69} = 3.529$, $p = 0.065$. Data are mean ± SEM. A posteriori tests were performed with the Tukey HSD procedure. *, different from the male incentive, $p < 0.05$, *** , $p < 0.001$. #, different from the same incentive in the other group, $p < 0.05$.

In females, chronic stress was associated with enhanced serum glucocorticoid concentration as well as with much facilitated sexual behavior (Williams et al., 1992). No facilitation was observed in adrenalectomized females (Gorzalka et al., 1998). Chronic administration of corticosterone to female rats also enhances all aspects of sexual behavior (Hanson et al., 1998). However, de Catanzaro (1987) found somewhat different effects when corticosterone was administered intracerebrally. In fact, inhibition was observed after chronic infusion into the preoptic area and the ventromedial hypothalamus. Acute administration of corticosterone lacks effect when the subcutaneous route is used (Gorzalka and Whalen, 1977), but stimulation of lordosis behavior is seen already 5 min after intravenous administration (Kubli-Garfias, 1990). Taken together, these data may suggest that glucocorticoids affect the long-term regulation of the activity of the sexual central motive state in female rats, whereas their role in short term regulation is unclear. Thus, variations in cortisol concentrations might explain part of the interindividual differences in the intensity of sexual motivation in female rodents. Whether this steroid is important for the intraindividual variation in sexual motivation is uncertain.

There is no human data available neither on the possible release of mineralocorticoids in conjunction with sexual activity nor on the effects of these steroids on sexual behavior. Animal data are also scarce, but one study showed that the administration of aldosterone does not affect

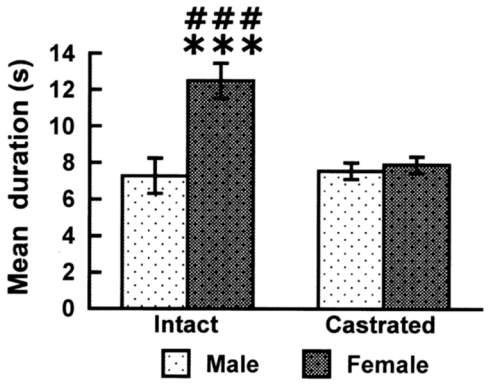


Fig. 6. Mean ± SEM duration of visits to the sexual and social incentives. Data are from the same rats that were used in the experiment illustrated in Fig. 5. It turned out that this variable had a distribution far from normality according to the Shapiro-Wilk test both for the social ($W_{71} = 0.834$, $p < 0.001$) and sexual incentive ($W_{71} = 0.730$, $p < 0.001$). Therefore, nonparametric tests were used. The Mann-Whitney U-test revealed that there was a difference between intact and castrated males with regard to the mean duration of visits to the sexual incentive, a sexually receptive female (U = 282, p < 0.001, Cohen's d = 1.08) but not with regard to the social incentive, another male (U = 607, p = 0.791, d = 0.063). We then compared the mean duration of visits to the social and sexual incentives in the intact males with the Wilcoxon test. There was a considerable difference (z = 5.153, p < 0.001, Cohen's d = 3.546). The mean duration of visits to the two incentives was similar in castrated males (z = 1.884, p = 0.06, d = 0.672). *** , different from the male incentive in the same group, $p < 0.001$; ###, different from the same sex incentive, the other group, $p < 0.001$.

female rat sexual behavior (Gorzalka and Whalen, 1977). We propose that mineralocorticoids do not play any significant role in the control of the sexual central motive state, neither in the long- nor in the short term.

6.3. Hypothalamic – pituitary hormones

6.3.1. Gonadotropins

The gonadotropins, particularly LH, are essential for the long-term regulation of the sexual central motive state because of their role in the control of the gonadal hormones. Similarly, gonadotropin releasing hormone (GnRH) is essential because of its regulation of the secretion of the gonadotropins. We have already discussed the gonadal hormones and will now limit ourselves to the other parts of the hypothalamus – pituitary – gonad axis. There is not much evidence showing that the gonadotropins themselves are involved in the central regulation of sexual responses, even though LH receptors are widely distributed in the brain, including areas important for sexual behavior (Blair et al., 2015). The central distribution of follicle stimulating hormone (FSH) and its receptor is less known, but both have been found in the hippocampus (Chu et al., 2008) and the cerebellum (Chu et al., 2013). The presence of FSH receptors have not been established in areas involved in sexual behavior, but neither has their absence. Regardless of this, the interest in elucidating the importance of the gonadotropins as transmitters rather than as hormones in the control of sexual behaviors has been limited. Nevertheless, a couple of studies have shown enhanced release of LH after copulation in male (e.g. Kamel and Frankel, 1978) as well as in female (e.g. Moss and Cooper, 1973; Peng et al., 1980) rodents. There is no evidence for FSH release during sexual interaction, neither in females nor in males (Kamel and Frankel, 1978). Consequently, it is possible that LH, but not FSH, is involved in the regulation of sexual responses in rodents. However, there are few data on the effects of LH or FSH administration in adult animals. We have been able to find only one study addressing this issue. Infusion of LH and FSH into the preoptic area or arcuate nucleus / ventromedial hypothalamus showed that FSH did not affect sexual behavior in female rats whereas LH had an inhibitory effect (Foreman and Moss, 1979). Whether this effect has any physiological relevance or not is difficult to judge, and we refrain from speculating about its possible role in the regulation of the momentaneous activity in the sexual central motive state.

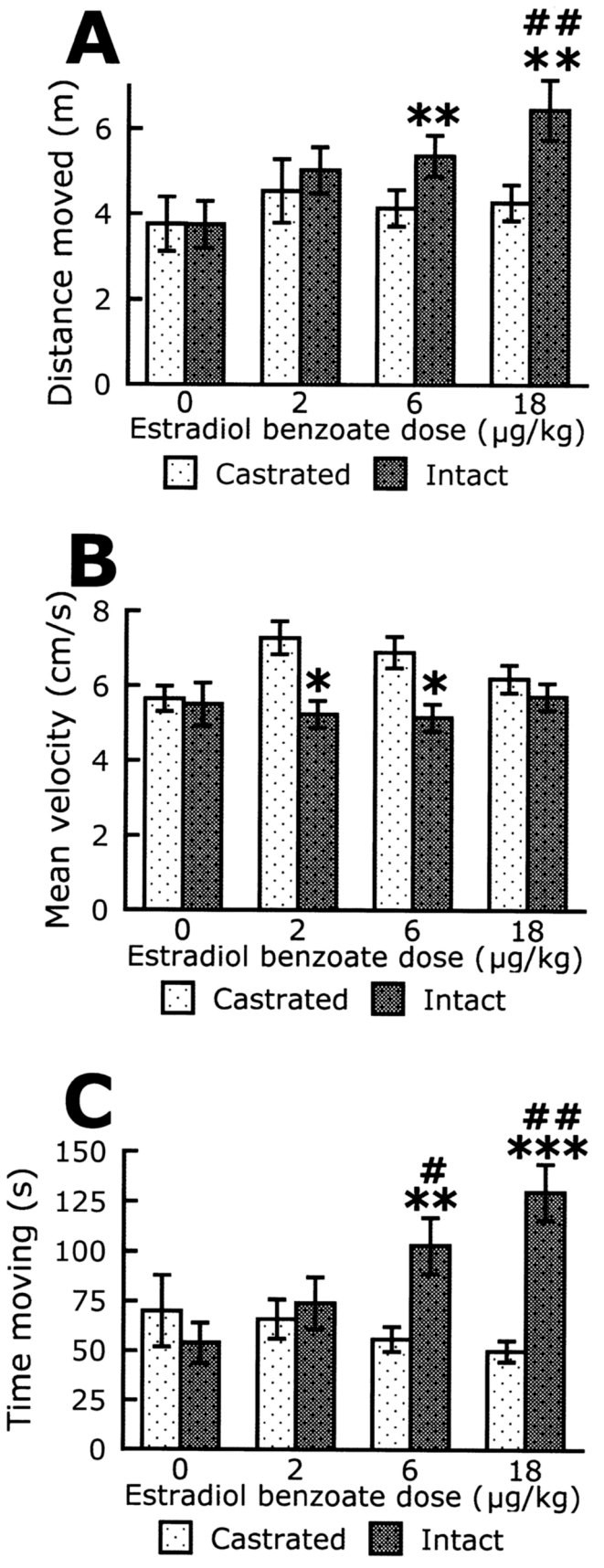
Sexual activity in the form of masturbation to orgasm leads to release of LH but not of FSH in women (Exton et al., 1999). However, coitus failed to alter plasma concentration of LH and FSH (Lee et al., 1974; Stearns et al., 1973). In men, LH and FSH concentrations were unaltered by sexual activity (Exton et al., 2001a; Krüger et al., 1998, 2003a). It appears that most data speak against any release of the gonadotropins in response to sexual incentive stimuli or sexual activity. Consequently, none of these hormones is likely to participate in the response of the sexual central motive state to these events in humans.

Enhanced general arousal did not affect LH release in female rats according to an old study (Neill, 1970). More recent data show that both acute and chronic stress, a state presumably associated with heightened arousal, reduces LH secretion in females (e.g. Li et al., 2006). There are also data showing that different stressors may have opposing effects on LH secretion. For example, serum LH is increased after daily sessions of restraint or mirror stress for 3 weeks, whereas intruder stress reduces LH (Nwogueze et al., 2021). Prolonged heat stress not only reduces LH concentration as expected, but also increases FSH concentration in serum (An et al., 2020). In male rats, acute stress leads to enhanced release of LH and FSH according to some reports (Armario et al., 1986b; López-Calderón et al., 1990). Chronic stress has the opposite effect on LH secretion, but FSH may be unaffected (Taché et al., 1978). It may be interesting to note that the classical arousal hormone, ACTH, is released proportionally to the intensity of the arousing stimulus whereas no such relationship is found with regard to LH release (Armario et al., 1986a). Furthermore, the fact that acute as well as chronic stress inhibit male rat sexual behavior (Retana-Marquez et al., 2003) while having opposite actions on LH secretion, at least in most studies, argues against any role for LH in the control of the sexual central motive state in male rodents. In females, restraint stress fails to alter sexual approach behaviors (Uphouse et al., 2008), despite the fact that LH concentration is modified. This observation suggest that possible effects of general arousal on LH release and subsequently on the sexual central motive state are slight, if any.

In women, acute as well as chronic stress have been reported to cause reduced vaginal response to sexual incentives (Hamilton and Meston, 2013; Ter Kuile et al., 2007), clearly suggesting that general arousal enhanced by stress has an inhibitory action on the sexual central motive state. Whether this is related to the effects of general arousal on LH or FSH secretion is unclear, however. In the Hamilton and Meston (2013) study, it was rather suggested that the reduced vaginal response was secondary to poor attention to the sexual incentive. Taken together, the data summarized above make us consider it unlikely that direct actions of LH or FSH in the brain are of any major importance for the sexual central motive state, neither in the long nor in the short term.

6.3.2. GnRH

GnRH administration has repeatedly been shown to enhance the intensity of sexual behavior in male and female rats (e.g. González-Flores et al., 2009; Moss et al., 1975; Saito, 1988, and references therein). This action seems to be localized to the brain, unrelated to potential effects on the release of pituitary or gonadal hormones (Pfaff, 1973; Sakuma and Pfaff, 1983). Therefore, GnRH acts as a neurotransmitter rather than as a hormone when affecting sexual behavior. In fact, GnRH receptors have been described in several structures important for responses to sexual incentives and for the display of copulatory activities (Jennes et al., 1988). Indeed, neurons expressing the GnRH receptor have been described in the preoptic area and ventromedial hypothalamus as well as in areas involved in the transmission of olfactory signals both from the main and accessory olfactory systems (Wen et al., 2011, see also Mucignat-Caretta, 2021). Consequently, it is possible to propose that GnRH contributes to the



(caption on next column)

Fig. 7. A. Mean ± SEM distance moved in the areas adjacent to the sexual (intact male) and social (castrated male) incentives in ovariectomized female rats (N = 15) treated with several doses of estradiol benzoate. Two-factor ANOVA with repeated measures on both factors, one being incentive (with the levels sexual and social) and the other being dose of estradiol benzoate (with the levels 0, 2, 6, and 18 µg/kg), was used. The data had previously been checked for normality, and the Mauchly test of sphericity yielded non-significant result. This applies to all variables illustrated in this figure. There was a main effect of dose, $F_{3,42} = 7.954$, $p < 0.001$, $\eta_p^2 = 0.362$; of incentive, $F_{1,14} = 7.368$, $p = 0.017$, $\eta_p^2 = 0.345$; and the interaction dose x incentive was also significant, $F_{3,42} = 3.499$, $p = 0.024$, $\eta_p^2 = 0.200$. Treatment with estradiol did not modify the distance moved close to the social incentive, but increased the distance moved close to the sexual incentive. B. The mean velocity of movement while moving in the females described in A. Main effect of dose, $F_{3,42} = 1.555$, $p = 0.214$; of incentive, $F_{1,14} = 15.375$, $p = 0.002$, $\eta_p^2 = 0.523$; interaction dose x incentive, $F_{3,42} = 2.653$, $p = 0.061$. The females moved faster when close to the castrated male than when close to the intact male after EB 2 and 6 µg/kg, while the speed of movement was unaffected by estradiol treatment. C. Time spent in movement in each of the incentive areas in these females. Main effect of dose, $F_{3,42} = 2.817$, $p = 0.051$; of incentive, $F_{1,14} = 8.048$, $p = 0.013$, $\eta_p^2 = 0.365$; interaction dose x incentive, $F_{3,42} = 4.454$, $p = 0.008$, $\eta_p^2 = 0.241$. It can be seen that the females do not distinguish the incentives when treated with oil or with 2 µg/kg of estradiol benzoate, whereas they move a lot more when close to the sexual incentive after the larger doses. *, different from the social incentive, $p < 0.05$, **, $p < 0.01$. #, different from oil, $p < 0.05$; ##, $p < 0.01$. These significances are based on tests for simple main effects and adjusted for multiple comparisons with the Sidak correction.

enhanced activity in the sexual central motive state caused by sexual incentives and the further increase during the execution of sexual acts. However, it appears that the response to a sexual incentive is not enhanced by infusions of GnRH into the 3rd ventricle of female rats whereas lordosis is facilitated (Dudley and Moss, 1985). It would appear that GnRH does not enhance the response to distant, sexually relevant stimuli causing approach, but facilitates the response to proximal sexual stimuli (tactile stimulation) causing the display of lordosis. Such a limited effect on the sexual central motive state coincides with studies showing that fos expression in Gn-RH neurons is increased by stimuli received during copulation in female rats whereas distant stimuli are ineffective (Pfaus et al., 1994). Actually, it appears that male ejaculation is needed for inducing fos-expression in GnRH neurons in females (Wu et al., 1992).

There are no data showing neither copulation-induced release of GnRH nor release caused by distant sexual incentives in male rats. A study in rabbits confirmed GnRH release during sexual activity in females, but found no release in males (Yang et al., 1996). Consequently, most data suggest that GnRH may be important for the momentaneous regulation of the activity in the sexual central motive state during copulation in females but not in males. This sexual dimorphism is difficult to explain. To complicate issues further, recent data show that female mice lacking GnRH neurons do not respond to distant stimuli from a male while copulating normally (Hellier et al., 2018), suggesting a role for the GnRH neurons exactly the opposite to the data reported by Dudley and Moss (1985). Considering the contradictory results, any definite conclusion as to the role of GnRH in the control of the sexual central motive state in rodents would be premature.

The effects of GnRH on genital responses to sexual stimuli in humans have not been studied. However, there are some questionnaire data that might be of interest. Sexual function was evaluated in patients diagnosed with Kallmann's syndrome, a hereditary condition often called hypogonadotropic hypogonadism. It is caused by deficient or no production of GnRH. All patients, male and female, were on hormone replacement therapy, maintaining blood hormone concentrations within the normal range. The lack of GnRH had no consequence for sexual functions in men, but women reported reduced sexual desire (Georgopoulos et al., 2018). A later, online study based on self-reported

diagnosis of hypogonadotropic hypogonadism showed lower sexual activity in male and female patients than in healthy controls (Kaluzna et al., 2021). Since the validity of this kind of online survey is questionable, these data might be suggestive, at most. In the absence of other studies having evaluated sexual functions in patients diagnosed with hypogonadotropic hypogonadism we conclude that GnRH has no or marginal effect on the sexual central motive state in men, whereas it may contribute to the momentaneous regulation of that state in women. It may be mentioned that GnRH stimulates the response to sexual incentives as well as the execution of copulatory acts in another female primate, the marmoset (Barnett et al., 2006), in line with our proposal concerning women.

The effects of altered general arousal on GnRH activity has not been systematically evaluated, neither in rodents nor in humans. We cannot, therefore, make any predictions concerning any possible contribution of GnRH to the increased activity in the sexual central motive state associated with enhanced arousal.

6.3.3. *Kisspeptin*

Kisspeptin is a peptide binding to the GPR54 receptor. Both the peptide and the receptor are widely distributed in the brain (Higo et al., 2016; Yeo et al., 2016). The main function of kisspeptin is to control the GnRH neurons, and it is, consequently, a major regulator of the hypothalamus – pituitary – gonad axis. In addition to its role in sexual functions and behavior, the peptide may be involved in the regulation of emotional behaviors such as fear and anxiety as well as in learning (reviewed in Mills et al., 2019). Because of the effects on the hypothalamic regulation of the gonadotropins and their regulation of the gonadal hormones, alterations in kisspeptin signaling has obviously consequences for sexual behavior. An important question is whether all actions of kisspeptin on sexual behavior can be explained by the endocrine effects, or if kisspeptin may alter this behavior independently of these effects. This question was addressed in an elegant study (Hellier et al., 2018), showing that the response to distant sexually relevant stimuli as well as lordosis were reduced in female mice lacking kisspeptin. Administration of kisspeptin restored these behaviors. When the females were made unable to synthesize GnRH, kisspeptin failed to restore the response to a distant sexual incentive (male odor). Treatment with GnRH reinstated the response, showing that the effects of kisspeptin on the response to distant sexual incentives depend on GnRH rather than on kisspeptin itself. However, lordosis was not reduced in the animals lacking GnRH, suggesting that kisspeptin affects this behavior independently of actions on GnRH neurons (Hellier et al., 2019, 2018). These observations suggest that kisspeptin stimulates activity in the sexual central motive state. Since exposure to sexual incentives causes enhanced expression of fos in kisspeptin neurons, it is possible that these neurons contribute to the increased activity in the sexual central motive state induced by sexual incentives. Thus, kisspeptin may affect the momentaneous activity of that state in female rodents. There are also data showing that kisspeptin is important for responses to sexual incentives in males. Distant sexual incentives enhance the number of fos-labeled kisspeptin neurons in the medial amygdala in male mice (Aggarwal et al., 2019). Moreover, when a drug acting at a designer receptor exclusively activated by designer drugs (DREADD) was used to stimulate kisspeptin neurons in the medial amygdala, enhanced preference for an estrous female was observed without any effect on copulatory behavior in male mice (Adekunbi et al., 2018). In view of these observations, we tentatively propose that kisspeptin contributes to the enhanced activity of the sexual central motive state caused by distant sexual incentives, but not to the further enhancement produced by the execution of copulatory acts.

Data concerning the role of kisspeptin in humans are not abundant. A peculiar study in young men evaluated the blood oxygen level dependent (BOLD) response to exposure to Chanel No. 5 perfume and pictures of female faces after intravenous administration of kisspeptin. Blood hormone concentrations were also determined. Kisspeptin increased the concentration of LH but not of testosterone or cortisol, at least not during the scanning period. Brain areas considered to be related to sexual motivation in humans (i.e. amygdala, insula, orbitofrontal cortex and thalamus) showed enhanced activity when exposed to perfume and to the female faces after kisspeptin administration (Yang et al., 2020). Whether the exquisite odor of Chanel's perfume is a sexual incentive or not is an open question. The same is the case for female faces. However, kisspeptin did not alter the BOLD response to pictures of food (Yang et al., 2021). This shows some specificity of the response. Similar results were obtained in another study, with explicitly sexual pictures as stimuli (Comninos et al., 2017). With good will, these results may be interpreted as suggesting that kisspeptin increases the response to sexual incentives in men, in the same way as it does in mice and rats. We have been unable to find any study evaluating kisspeptin effects on responses to sexual stimuli in women. Nevertheless, we venture to propose that kisspeptin has some role in the momentaneous control of the activity in the sexual central motive state in both men and women.

Intracerebroventricular administration of kisspeptin enhances general arousal in male rats (Csabafi et al., 2013). In female kisspeptin knockout mice arousal is reduced compared to the wildtype (Tolson et al., 2014). Whether arousal modifies kisspeptin release is not known. We have not been able to find any data on the relationship between kisspeptin levels and general arousal in humans. Thus, it is impossible to speculate about any involvement of kisspeptin in the effects of general arousal on the sexual central motive state.

6.3.4. *Prolactin*

Prolactin is a pituitary hormone known to be released during sexual activity in male and female rats. In males, one study show that prolactin is released already after one intromission (Kamel et al., 1975). Post-ejaculatory release was larger, though. Another study established that ejaculation is required (Oaknin et al., 1989). In mice, the hormone is released after ejaculation but not during the preceding part of sexual interaction (Bronson and Desjardins, 1982) according to one study whereas ejaculation was not necessary in another (Valente et al., 2021). Female rats also release prolactin after copulation or artificial vaginocervical stimulation (Gunnet and Freeman, 1983). Whether this release has any behavioral consequence or not is uncertain. The effects of experimental manipulations of central or peripheral prolactin levels have been contradictory. Intracerebroventricular injection of prolactin as well as hyperprolactinemia caused by pituitary transplants under the renal capsule inhibit lordosis (Dudley et al., 1982). Prolonged hyperprolactinemia induced by domperidone impairs sexual behavior in male rats (Bailey and Herbert, 1982) whereas acute hyperprolactinemia has no effect (Nasello et al., 1997). Pharmacological manipulations of prolactin release also fail to alter copulatory behavior in male mice (Valente et al., 2021). Subcutaneous injection of prolactin has an immediate stimulatory action on male as well as on female sex behavior (Drago and Lissandrello, 2000). These conflicting observations make it impossible to speculate about the role of prolactin in the control of the activity of the sexual central motive state in rodents.

Prolactin is released after orgasm in men and women (Exton et al., 2001b). Sexually relevant stimuli such as pornographic movies do not affect prolactin blood concentration (Exton et al., 2000b; Heiman et al., 1991; Krüger et al., 2003a). It has been reported that the subjective quality of orgasm in young women is associated with the change in prolactin concentration between a pre- and a postcoital blood sample, whereas penile-vaginal intercourse without orgasm did not affect prolactin release (Leeners et al., 2013). Since prolactin release seems to depend on the presence of orgasm, an event reducing sexual motivation, it is unlikely that prolactin enhances the activity in the sexual central motive state. To the contrary, prolactin may be related to the reduction in sexual motivation following orgasm. Indeed, pharmacological manipulation of prolactin concentration in the blood of young men exposed to a pornographic movie showed that reduced concentration enhanced sexual motivation as evaluated by a questionnaire. Increased

prolactin concentration had no significant effect on motivation but prolonged the ejaculation latency (Krüger et al., 2003b). However, the penile response to a pornographic movie is unaltered in men diagnosed with severe hyperprolactinaemia (Carani et al., 1996). In premenopausal women, severe hyperprolactinemia reduces sexual functions, including desire according to questionnaire data. No other hormonal changes in these patients were associated with sexual dysfunction (Kadioglu et al., 2005). It might be added that blood prolactin concentration is negatively correlated with sexual desire in postmenopausal women (Laan and van Lunsen, 1997). The dopamine D_2 agonist cabergoline has been found to improve sexual desire in men and women with hyperprolactinemia, and the improvement was correlated with the reduction in blood prolactin concentration (Krysiak and Okopien, 2019). These observations suggest that prolactin decreases the activity in the sexual central motive state in men and women. In fact, this may be related to the cessation of sexual activity after orgasm. Incidentally, a multiorgasmic man was found not to release prolactin even after three orgasms (Haake et al., 2002), and in women masturbating to repeated orgasms, there is a gradual increase in prolactin concentration after each orgasm. These observations strengthen the hypothesis of an inhibitory action of prolactin on the sexual central motive state.

Aversive stimuli such as footshock (Grandison and Guidotti, 1977) or restraint (Samson et al., 1985; Van Vugt et al., 1978) cause immediate release of prolactin from the pituitary in male rats. Furthermore, prolactin blood concentration has been shown to depend on the intensity of the stressor (Armario et al., 1986a; Kant et al., 1983). Assuming that stress enhances general arousal, it can be concluded that prolactin release is one of the many effects of increased arousal. The data reported above refer to peripheral prolactin. Possible actions on the sexual central motive state are probably localized to the central nervous system. It is known that prolactin immunoreactivity as well as prolactin receptors are widely distributed in the brain. Both are found in structures important for male and female sexual behaviors, such as the bed nucleus of the stria terminalis, amygdala, the central gray, hypothalamus and the olfactory bulb (reviewed in Freeman et al., 2000). Pituitary prolactin can bypass the blood-brain barrier through the choroid plexi and reach the brain via retrograde blood flow from the pituitary to the hypothalamus (Oliver et al., 1977). There is also evidence showing that immobilization stress enhances prolactin release from and synthesis in hypothalamic neurons (Torner et al., 2004). However, more recent data suggest that local synthesis of prolactin within the brain might be of minor importance compared to prolactin entering from the systemic circulation (reviewed in Bridges and Grattan, 2019). Considering that enhanced general arousal as well as sexual activity causes prolactin release in rodents, and that systemic prolactin has access to prolactin receptors within the brain, we can propose that this peptide may modulate the momentaneous activity of the sexual central motive state. The postorgasmic prolactin increase could reduce activity in the sexual central motive state, hence sexual motivation, and explain the subsequent cessation of sexual activity. Unfortunately, this proposal does not coincide with the data showing that stress (enhanced general arousal) also leads to prolactin release. Both humans and rodents respond with enhanced sexual motivation to enhanced general arousal, as mentioned in Sections 5.3 and 5.4. Perhaps the data showing that pharmacological manipulation of prolactin fails to alter the postejaculatory interval in mice can be generalized to other species. In view of these contradictions, we refrain from making any conclusion as to the role of prolactin in the short-term or momentaneous regulation of the sexual central motive state.

6.3.5. Oxytocin

The nonapeptide oxytocin is released from the neurohypophysis into the blood stream in response to mechanical stimulation of the nipple. Due to actions on the myoepithelial cells in the breasts, milk is expelled (Brown et al., 2013). Besides this well-established function, oxytocin is also widely distributed in the brain, and oxytocin receptors are found in many areas (reviewed in Jurek and Neumann, 2018). In fact, it seems that oxytocin acts as a neurotransmitter in addition to acting as a hormone. The potential central nervous effects of oxytocin could be of importance for the regulation of the activity of the sexual central motive state.

In rodents, oxytocin is released in the brain during sexual behavior. In male rats, copulation leads to enhanced release in the paraventricular nucleus (Waldherr and Neumann, 2007). The simple exposure to a sexually receptive female did not lead to any significant oxytocin release. Unfortunately, the data reported do not allow for a distinction between pre- and postejaculatory release. Similarly, in female rats oxytocin is released during mating (Nyuyki et al., 2011), but the microdialysis procedure does not offer sufficient temporal resolution to associate release with any particular behavior. Data from prairie voles (*Microtus ochrogaster*) show that females exposed to an inaccessible male did not release oxytocin. Likewise, females failing to mate when allowed to freely interact with a male did not release oxytocin, whereas mating females did (Ross et al., 2009). We interpret these data as showing that sexual incentives do not lead to enhanced release of oxytocin whereas the performance of an unknown amount of copulatory acts do. Considering this, it is unlikely that oxytocin contributes to the stimulation of the sexual central motive state caused by sexual incentives. Depending on the timing of the release, oxytocin could either contribute to the increase in arousal occurring during copulation, or to the reduced arousal following ejaculation in the male and following the receipt of an ejaculation in the female.

In male mice, a social stimulus (a juvenile of unspecified sex) has been found to increase activity in oxytocinergic neurons in the paraventricular nucleus. Chemogenetic stimulation of these neurons enhanced sociability whereas inhibition had the opposite effect (Resendez et al., 2020). The fact that oxytocin may be involved in social motivation does not constitute any evidence for a role in sexual motivation, unfortunately.

Pharmacological studies have shown that administration of oxytocin agonists and antagonists stimulate and reduce sexual behavior, respectively (reviewed in Argiolas and Melis, 2013; Veening et al., 2015). Further support for a role of oxytocin in sexual behavior come from studies in female knockout mice lacking the peptide. Intact, cycling females tested in the proestrus phase of the estrous cycle show reduced lordosis in response to the mounting male (Becker et al., 2013, the same data also reported in Zimmermann-Peruzatto et al., 2017). To the contrary, the sexual behavior of male knockout mice is similar to that of the wildtype (Lazzari et al., 2013). The sex difference in the effects of oxytocin knockout on copulatory behavior has been confirmed (Dhungel et al., 2019). However, when the response to distant sexually relevant stimuli was evaluated, it turned out that both male and female knockout mice were far inferior to the wildtype (Dhungel et al., 2019). This coincides with data from male rats and mice, in which an oxytocin antagonist reduces approach to sexually receptive females (Blitzer et al., 2017; de la Zerda et al., 2020, but see Le Moëne and Ågmo, 2018b for a negative result). In females, oxytocin seems to play a role in the regulation of copulatory behavior. In both sexes, oxytocin may be involved in the responses to distant, sexually relevant stimuli. Considering that oxytocin is not released in response to distant sexual stimuli, it is difficult to understand how this peptide could be of importance for the response to them. This also applies to copulatory behavior. Even though the exact moment of oxytocin release during the course of rodent sexual behavior has not been determined, there is no compelling reason to believe that it should be different from humans (see below), i.e. oxytocin is released during and after orgasm. Since this event is followed by reduced sexual motivation, it is quite unlikely that oxytocin enhances activity in the sexual central motive state. Therefore, we conclude that data are too contradictory to make possible any proposal as to the role of oxytocin in the control of the sexual central motive state in rodents.

In men and women, blood oxytocin concentration is increased after masturbation to orgasm whereas the preorgasmic increase is

nonsignificant (Carmichael et al., 1987; Murphy et al., 1987). When actual copulation replaced masturbation, increase in blood oxytocin concentration was found in orgasmic women while no change was observed in anorgasmic women (Caruso et al., 2018). The importance of orgasm for oxytocin release was confirmed in a recent review (Cera et al., 2021). Since it seems to be generally accepted that oxytocin is released at orgasm in men and women, it would be reasonable to propose that the hormone (acting as a neurotransmitter) is associated with the postorgasmic decline in sexual motivation. Strangely enough, most of the studies that have been made on oxytocin effects on sexual motivation and behavior presupposes a stimulatory action of the hormone. However, intranasal oxytocin to women with sexual dysfunction does not improve any questionnaire measure of sexual functioning (Muin et al., 2015). This is also the case in healthy men and women (e.g. Behnia et al., 2014; Burri et al., 2008). Furthermore, a laboratory study of the vaginal response to a pornographic movie segment failed to detect any effect of intranasal oxytocin (Krüger et al., 2018). Despite the many claims to the contrary (e.g. Lee et al., 2009), systematic evaluations of oxytocin effects on human sexual motivation and behavior show that such effects are slight or entirely absent. Thus, there is not much reason to believe that oxytocin alters the activity of the sexual central motive state. The release after orgasm has probably consequences unrelated to the sexual behavior itself. For example, oxytocin produces intense contraction of the distal duct of the epididymis, and could be important for sperm transport during ejaculation (Stadler et al., 2021).

General arousal has been found to enhance oxytocin release in rats (Onaka and Yagi, 1990) as well as in men and women (Alley et al., 2019; Pierrehumbert et al., 2010). At present, it is impossible to determine whether this release has any effect on the sexual central motive state.

6.3.6. *Melanocortins*

The heptapeptide Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-OH, generic name bremelanotide, is a nonspecific melanocortin receptor agonist. It has been reported to enhance female rat paracopulatory behaviors without affecting lordosis responses (Pfaus et al., 2007, 2004), and was found to have some effects on sexual desire in women (Kingsberg et al., 2019). Specifically, the reported effect consisted of a higher score on the female sexual function index – desire domain (FSFI-D; Rosen et al., 2000) in women treated with the peptide than in women given placebo. The two items evaluating this domain are:

1) Over the past 4 weeks, how often did you feel sexual desire or interest?

2) Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest? (Rosen et al., 2000, p. 205)

An increase in the score derived from these questions is suggestive of a stimulatory action on the sexual central motive state. In female rats, the endogenous ligand, α-melanocyte stimulating hormone, has been found to facilitate lordosis without affecting sexual approach behaviors (Gonzalez et al., 1996).

The clinical data mentioned above have been questioned (Spielmans, 2021), and it is quite possible that bremelanotide does not improve female sexual arousal/interest disorder, in contrast to the claims made by the manufacturer. The contradictory data from female rats combined with the doubtful effects of bremelanotide in women preclude any conclusion as to the role of the α-melanocyte stimulating hormone and other ligands at the melanocortin receptors in the control of the sexual central motive state.

In male mice, reduced production of α-melanocyte stimulating hormone (α-MSH) is associated with deficient sexual behavior (Faulkner et al., 2015). A melanocortin 4 antagonist has been reported to reduce sexual behavior in male rats (Caquineau et al., 2006), and mice lacking the melanocortin 4 receptor have prolonged ejaculation latency (Semple et al., 2019). In men, melanocortin 4 agonistsagonizts have been tested as treatment for erectile dysfunction (Diamond et al., 2004; Lansdell et al., 2010). There is no indication that other manifestations of sexual motivation are affected, though. It appears that melanocortins may enhance activity in the sexual central motive state in male rodents and perhaps also in men. However, this proposal needs more data before it can be considered more than a qualified guess.

6.3.7. *Other peptides*

Several other peptide hormones, some of them also considered to be neurotransmitters, as well as non-hormonal peptides have been implicated in the control of sexual motivation and behavior. Available data are not sufficient for evaluating their potential role in the regulation of the sexual central motive state. Release patterns are often unknown, and systematic pharmacological data are often lacking. This can easily be confirmed by consulting some of the many excellent reviews of this subject (e.g. Argiolas and Melis, 2013; Dornan and Malsbury, 1989). Nevertheless, future studies may show that some of these peptides are indeed involved in the regulation of the sexual central motive state.

6.4. *Classical transmitters*

Many of the classical neurotransmitters have been suggested to modify rodent sexual motivation (see Argiolas, 1999; Bitran and Hull, 1987, for reviews), and there are scattered reports about drug effects in humans (e.g. Clayton et al., 2016; Rosen and Ashton, 1993). Nevertheless, it is difficult to attribute any definite function in the control of the sexual central motive state to any of these transmitters, although speculations have been made. It appears that dopamine has been the favorite for these speculations, at least as far as male and female rodents are concerned. A careful analysis of the many conflicting observations reported in the literature suggested that dopamine involvement is limited to effects on general arousal (Paredes and Ågmo, 2004). Notwithstanding, the fact that male rats (Hull et al., 1995) and quails (Ball and Balthazart, 2011; Kleitz-Nelson et al., 2010) who fail to release dopamine in the nucleus accumbens in response to a female will not initiate copulation has been interpreted to mean that dopamine release is crucial for sexual responses. Sexual incentives (e.g. Fujiwara and Chiba, 2018; Wenkstern et al., 1993) and copulation enhance dopamine release in the nucleus accumbens (e.g. Damsma et al., 1992; Mas et al., 1990; Robinson et al., 2001) and elsewhere in the brain (e.g. Hull et al., 1993; Melis et al., 2003; Sanna et al., 2017), and this release is believed to enhance activity in the sexual central motive state, and cause sexual approach and eventually copulation. This argument is complicated by the fact that dopamine may be released because of the heightened arousal in the responding males rather than causing the heightened arousal and ensuing sexual responses. Thus, it is an open question whether enhanced dopamine release is the cause or consequence of the momentarily increased sexual motivation and general arousal observed during exposure to sexual incentives. In fact, dopamine antagonists do not reduce, and agonists do not enhance, sexual approach behaviors in male rats (Ågmo, 2003a). However, male rats lacking the dopamine transporter show facilitated sexual behavior together with much enhanced dopamine concentrations in the brain (Sanna et al., 2020). There is no dopamine response to sexual incentives in these animals, and only prolonged copulation led to enhanced release. The chronically enhanced dopamine availability, together with the facilitated sexual behavior, could indicate that dopamine contributes to the long term regulation of activity in the sexual central motive state. At the same time, the lack of dopamine release when exposed to sexual incentives indicate that dopamine is unrelated to the behavioral response to these incentives. This is exactly the opposite to the proposal mentioned some paragraphs ago, namely that enhanced dopamine release is a requisite for initiating sexual behavior. Even in the unlikely case that dopamine

release were the cause of the initiation of sexual activity in male rats, it remains to determine why dopamine is released in some males and not in others.

In female rats, dopamine is also released at several brain sites in response to sexual incentives (e.g. Pfaus et al., 1995) and during sexual activity (e.g. Becker et al., 2001; Jenkins and Becker, 2003). Dopaminergic drugs have been reported to have all kinds of effects in female rodents, but all these effects can be attributed to alterations in general arousal or motor function (Paredes and Ågmo, 2004). Furthermore, dopaminergic drugs are ineffective in a procedure designed for the evaluation of sexual incentive motivation (Ellingsen and Ågmo, 2004). As is the case in males, the possible role of dopamine in the inter- and intraindividual differences in female rodent sexual behavior remains unknown.

It has already been mentioned that enhanced general arousal is associated with dopamine release (reviewed in da Silva et al., 2018; Liu et al., 2021, among many others). Pharmacological data show that increased dopaminergic activity leads to increased arousal, for example augmented locomotor activity, whereas reduced dopaminergic activity leads to low levels of general arousal. We propose that dopamine may enhance activity in the sexual central motive state in rodents indirectly, via actions on general arousal.

Serotonin is another monoamine that has been implicated in sexual motivation. Due to the multitude of serotonin receptors (15 has been described so far) and the diversity of effects seen after blocking or stimulating them (Deka et al., 2020), it would be unfeasible to provide a review of all the effects described. A simplified account could be limited to mentioning that there is substantial evidence suggesting an inhibitory role for serotonin in male and female rat copulatory behavior (reviewed in Ahlenius, 1993; Bitran and Hull, 1987). The effects of serotonergic agents on sexual approach behavior have been little studied. In fact, none of the many drugs specific for serotonin receptor subtypes has been tested for effects on sexual approach. However, there are some data concerning the consequences of chronic treatment with selective serotonin reuptake inhibitors. Sexual approach is inhibited both in male (Cantor et al., 1999) and female (e.g. Kaspersen and Ågmo, 2012) rats. All these observations suggest that serotonin reduces the activity of the sexual central motive state, hence sexual motivation, and performance in rodents. However, the fact that serotonin is not released in areas important for sexual behavior (Lorrain et al., 1998) makes it unlikely that serotonin participates in the physiological regulation of the sexual central motive state.

In humans given selective serotonin reuptake inhibitors for the treatment of depression, sexual side effects are not uncommon (La Torre et al., 2013a,b; Rosen et al., 1999). However, in healthy young men, neither fluoxetine nor citalopram has been reported to have any significant effect on sexual motivation as evaluated by questionnaires (Madeo et al., 2008). There are no human studies in which objective measures of sexual motivation after treatment with serotonergic agents have been employed. Until additional data as to the effects on sexual functions of manipulations of serotonergic systems in healthy humans have become available, we refrain from proposing any conclusion.

Besides the occasional interest in serotonin, there has been very limited efforts to discover the transmitters involved in the response of the sexual central motive state to sexual incentives in healthy humans. Even less interest has been shown for explaining individual differences in the sexual central motive state in terms of transmitters. Likewise, speculations around the transmitters involved in the momentaneous control of human sexual motivation are rare and often unfounded. Nevertheless, a series of thorough reviews of several classes of drugs (La Torre et al., 2013a, 2013b, 2016, 2015, 2014) concluded that it would be premature to make any definite proposal as to the role of specific transmitters in the control of human sexual functions. More recent imaging studies (reviewed in Graf et al., 2019) report some effects of several kinds of drugs on the hemodynamic response to sexual stimuli, but since no objective measure of sexual motivation was included, the reported effects are difficult to interpret in motivational terms. It seems that the role of classical transmitters in the short- and long-term control of sexual motivation is just as mysterious in humans as it is in rodents.

6.5. Conclusion

The basic activity of the sexual central motive state manifests itself in the responsiveness to sexual incentives. This responsiveness is presumably a stable trait. We suggest that the long-term regulation of the sexual central motive state depends on gonadal hormones in both rodents and humans. However, these hormones seem to have a permissive action, in the way that once the concentration is above some threshold, further increases in hormone availability do not affect the motivational state. Search for factors beyond plasma concentration of the gonadal hormones have proved unsuccessful. The expression of several genes important for sexual behavior in several brain areas does not vary systematically between male rats displaying different levels of sexual activity, for example (Trejo-Sanchez et al., 2020). Among the genes studied were the androgen and estrogen receptors, aromatase, and two types of DNA methyltransferase. The importance of androgen and estrogen receptors as well as of aromatase for sexual behavior was established long ago, whereas the role of DNA methylation started to become evident during the last decade. Several enzymes are responsible for methylation of the cytosine residue in the DNA molecule, among those DNA-methyltransferase 3α and DNA methyltransferase 1. The degree of methylation determines the rate of transcription. DNA methylation has been found to be important for sexual differentiation (McCarthy and Nugent, 2015), and in human adolescents hypomethylation of the CALM3 gene is associated with risky sexual behaviors (de Vocht et al., 2018). This gene codes for the protein calmodulin-like protein 3, which is a coregulator of the estrogen receptor α (Qin et al., 2017). Thus, the Trejo-Sanchez et al. (2020) study included most of the genes crucial for the endocrine regulation of sexual motivation and behavior. Their conclusion, that individual differences in rat sexual motivation and behavior are not associated with specific brain characteristics, seems entirely justified. Whether this holds also for other male mammals and for females is not known, but there is no a priori reason to think that it would not. The long-term regulation of the basic activity of the sexual central motive state remains mysterious, and so does the cause of interindividual differences.

Sexual incentives will enhance activity in the sexual central motive state. Compounds that can be involved in this incentive-induced enhanced activity must be released when the subject is exposed to an incentive. Thus, the first step in any organized effort to understand the neurobiology of the sexual response would be to identify these compounds. However, that a compound is released in response to a sexual stimulus does not by itself constitute evidence for an effect on the sexual central motive state. Release could be an epiphenomenon without consequences. The absence of release, to the contrary, is sufficient evidence for concluding that the compound cannot be important for the response to sexual incentives. If a compound is released, then it must be shown that experimental manipulations of the availability of the compound indeed alters the sexual central motive state. Such manipulations can be local or systemic administration of the compound itself or of agonists or antagonists. Opto- or chemogenetic procedures could also be used for stimulating or reducing release from neurons or glia. Alternatively, genes coding for the compound, or for a component necessary for its synthesis or release, could be inactivated in some way or another. If a component is released in response to sexual incentives, and the activity in the sexual central motive state is altered by any of the manipulations above, then, and only then, can we conclude that the compound is important for the short-term or momentaneous regulation of sexual motivation.

As can be seen in Table 2, few if any compound satisfies the criteria outlined in the preceding paragraph. There are some scattered coincidences, but there are always some contradictory observation. We are

Table 2
Hormones and transmitters potentially involved in the control of the activity in the sexual central motive state. +, stimulatory action or enhanced release during sex; -, inhibitory action; 0, no effect or no release during sex; ?, insufficient or no data available. For supporting references, see text.

Hormone	Effects in males				Effects in females			
	Long-term control	Release caused by sex	Immediate effect	Release during general arousal	Long-term control	Release caused by sex	Immediate effect	Release during general arousal
Testosterone rat	+	+	?	?	0	0	0	?
Testosterone human	+	?	?	?	+	?	0	?
Estradiol rat	+	?	+	?	+	0	0	?
Estradiol human	0	0	0	?	0	0	0	?
Cortisol rat	0	+	0	+	+	+	?	+
Cortisol human	0	0	0	+	0	0	0	+
LH rat	+[a]	+	?	?	+[a]	+	–	?
LH human	+[a]	0	0	?	+[a]	0	0	?
FSH rat	0	0	0	0	0	0	0	0
FSH human	0	0	0	0	0	0	0	0
GnRH rat	+[a]	?	?	?	+[a]	+	?	?
GnRH human	+[a]	?	0	?	+[a]	?	+	?
Kisspeptin rat	+[b]	+	+	?	+[b]	+	+	?
Kisspeptin human	+[b]	?	+	?	+[b]	?	?	?
Prolactin rat	0	+	?	+	0	+	?	+
Prolactin human	0	+	–	+	0	+	–	+
Oxytocin rat	0	+	+	+	0	+	+	+
Oxytocin human	0	+	0	+	0	+	0	+
Melanocortins rat	0	?	+	?	0	?	+	?
Melanocortins human	0	?	+[c]	?	0	?	?	?
Dopamine rat	0	+	+[d]	+	0	+	+[d]	+
Dopamine human	0	?	?	+	0	?	?	+

[a] Probably mediated by the gonadal hormones.
[b] Probably mediated by GnRH – gonadotropins – gonadal steroids.
[c] Effect limited to facilitated erection.
[d] Both stimulatory and inhibitory effects of dopaminergic agents have been reported.

forced to conclude that the short-term or momentaneous regulation of the activity of the sexual central motive state is essentially unknown. This conclusion also applies to the modulatory role of general arousal.

7. Sexual and general arousal are intrinsically associated

In the preceding overview, we have tried to ascertain the potential role of several compounds in the long- and short-term control of sexual motivation, i.e. the activity of the sexual central motive state. Furthermore, we have described how these compounds may be affected by general arousal. One purpose was to find out whether there is a bidirectional relationship between actions on sexual motivation and actions on general arousal. Table 2 summarizes the results of this analysis. It appears that there is not any necessary coincidence between release caused by general arousal and effects on the central motive state neither in rodents nor in humans. Since data concerning the effects of altered general arousal on release of many of the compounds listed in Table 2 are lacking, this is a tentative conclusion. It may also be observed that the compounds known to be released during sex are also released by enhanced general arousal. This is not surprising, since sex enhances general arousal.

We have presented abundant evidence showing that whenever sexual responses are activated, general arousal is also increased. We have also shown that some compounds released during the exposure to sexual incentives simultaneously enhance sexual and general arousal. This coincidence is not surprising. In rats and humans, copulatory behavior involves substantial physical activity, in the form of coordinated activity in skeletal muscles. The level of general arousal is an important determinant of that activity. At the same time, copulation requires a series of specific genital responses. The main genital response in males is erection, in the human an entirely vascular response. In the rat, vascular erection is reinforced by contraction of the striated penile muscles. Furthermore, in the rat, activity in these muscles is necessary for achieving vaginal penetration, and they will also contribute to the expulsion of semen at ejaculation in rats and men. During the first phase of ejaculation, seminal emission, smooth muscles in the epididymis and vas deferens will propel spermatozoa into the urethra while other smooth muscle cells will expel the contents of the seminal vesicle and the prostate. These contents will form the bulk of the ejaculate. In females, the main genital responses are clitoral engorgement and vaginal lubrication. Interestingly, there is some evidence suggesting that these sexual responses may be activated outside of sexual contexts by extreme levels of general arousal (Sachs, 2007, 2008). What we could call "effective sexual motivation", or momentaneous activity level in the sexual central motive state, is always a combination of sexual and general arousal, as we try to illustrate in Fig. 1. We have found no evidence for any difference between humans and rodents in this respect.

8. Are the differences between rats and humans more than trivial?

Another purpose with the description of the hormonal and transmitter responses to sexual stimuli or sexual activities or changes in the level of general arousal was to compare rodents and humans. Similarities would strengthen the popular notion that rodents can be used to predict effects of drugs on human sexual functions (Ågmo, 2014; Ågmo et al., 2004; Le Moëne and Ågmo, 2019). Important dissimilarities would question that notion. The summaries presented in Tables 1 and 2 clearly suggest a strong similarity between rodents and humans. The neurochemical control of the sexual central motive state seems to have been highly conserved among mammals, and it should, consequently, be possible to make reliable predictions from one mammalian species to another.

9. General conclusions

When we want to make comparisons between species, it is necessary to have a common framework within which to make these comparisons.

We believe that the incentive motivational model provides a useful framework. There are several reasons for this. One is historical continuity. Already the earliest, and enormously influential, analyses of sexual motivation incorporated the notion of a somewhat dormant state that needed to be activated by appropriate stimuli (McDougall, 1914, 1926), or by an internal drive that could be reinforced by appropriate sensory stimulation (Freud, 1905, 1915). The notion that sexual incentives are important for activating sexual motivation was not only apparent for the pioneers. It has been pointed out many times since (Ågmo, 1999, 2007; Beach, 1956; Toates, 2009). The incentive motivation model used here is nothing more than an illustration of linear progress in the field of sexual motivation.

Another advantage of the present incentive motivation model resides in the use of the concept "central motive state". This has an enormous explanatory power when it comes to account for both the long-term and fast variations in the intensity of sexual motivation. With an incentive stimulus and a central motive state we have all the necessary ingredients for explaining the mysteries of sexual motivation. Thus, the model is parsimonious in agreement with the classical requirements of William of Occam. It is not easy to see how either the incentive stimulus or the central motive state could be removed from the model without a serious loss of explanatory power. Likewise, it is not easy to see how additional concepts could enhance explanatory power. Finally, the model can easily interact with non-sexual elements, like general arousal, thereby further increasing its explanatory power.

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