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Pharmacological and physiological aspects of sexual exhaustion in male rats

ALONSO FERNÁNDEZ-GUASTI and GABRIELA RODRÍGUEZ-MANZO

Departamento de Farmacobiología, Cinvestav, Mexico

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The present article reviews the current findings on the interesting phenomenon of sexual satiety. Knut Larsson in 1956 reported on the development of sexual exhaustion in the male rat after repeated copulation. We have studied the process and found the following results. (1) One day after 4 hours of *ad libitum* copulation, two-thirds of the population showed complete inhibition of sexual behavior, while the other third displayed a single ejaculatory series from which they did not recover. (2) Several pharmacological treatments, including 8-OH-DPAT, yohimbine, naloxone and naltrexone, reverse this sexual satiety, indicating that the noradrenergic, serotonergic and opiate systems are involved in this process. Indeed, direct neurochemical determinations showed changes in various neurotransmitters during sexual exhaustion. (3) Given enough stimulation, by changing the stimulus female, sexual satiety was prevented, suggesting that there are motivational components of the sexual inhibition that characterizes sexual exhaustion. (4) The GABA antagonist bicuculline, or the electrical stimulation of the medial preoptic area, did not reverse sexual exhaustion. These data suggest, on the one hand, that sexual exhaustion and the postejaculatory interval (which is shortened by bicuculline administration) are not mediated by similar mechanisms and, on the other, that the medial preoptic area does not regulate sexual satiety. (5) The androgen receptor density in brain areas closely related to the expression of masculine sexual behavior, such as the medial preoptic nucleus, was drastically reduced in sexually exhausted animals. Such reduction was specific to certain brain areas and was not related to changes in the levels of androgens. These results suggest that changes in brain androgen receptors account for the inhibition of sexual behavior present during sexual exhaustion. (6) The recovery process of sexual satiety after 4 hours of *ad libitum* copulation reveals that, after 4 days, only 63% of the males are able to show sexual behavior while after 7 days all animals display copulatory activity.

Key words: Sexual satiety, sexual exhaustion, motivation, postejaculatory interval, brain androgen receptors.

Dr Alonso Fernández-Guasti, Departamento de Farmacobiología, Cinvestav, Calz. De los Tenorios 235, Col. Granjas Coapa, Mexico 14330 D.F., Mexico. E-mail: jfernand@mail.cinvestav.mx

Knut Larsson published in 1956 his excellent thesis on the sexual behavior of the male albino rat, in which a thorough revision of all aspects of this behavior was conducted (Larsson, 1956). The careful and systematic study of the laboratory rat's male sexual behavior in this thesis, including the analysis of the laboratory conditions, the methods of observation and the influence of factors such as age, endocrine stage and diurnal variations, provided a valuable basis that allowed progress in this field. Knut Larsson included a chapter in that thesis describing the process of sexual satiation.

Sexual exhaustion or sexual satiation is a phenomenon that appears after repeated ejaculation. The main feature of this phenomenon is the natural instatement of a long-lasting inhibition of sexual behavior. The exhaustion phenomenon was described in male rats (Beach & Jordan, 1956; Larsson, 1956) and interest centred on the male's copulatory performance and capacity. Thus, the study of the development, recovery and influence of external stimuli on the sexual capacity and performance of males characterized the initial approaches to the phenomenon. Although most of the data regarding sexual exhaustion have been obtained in rats, the phenomenon has also been described for other mammalian species, including hamsters (Beach & Rabedeau, 1959; Bunnell *et al.*, 1976), rhesus macaques (Bielert & Goy, 1973; Phoenix & Chambers, 1988) and bulls (Almqvist & Hale, 1956).

SEXUAL EXHAUSTION: DEVELOPMENT AND RECOVERY

Knut Larsson described in his thesis the features of sexual satiation based on a series of experiments performed in 1954. In the first experiment he analyzed the effects of mild sexual activity on further sexual behavior. The experimental schedule was as follows. Sexually experienced males were allowed one hour of sexual activity every fourth day three times, followed by additional sexual behavior for one hour every third day four times. Male sexual behavior was recorded on the last test of each schedule segment. Finally, they were allowed to recover for one month and recorded for sexual behavior once more.

The results of this experiment were summarized by Knut Larsson as follows:

Sexual satiation occurred when the animals were not allowed to recover from one hour of activity. It was characterized by the following changes:

(1) A diminished number of ejaculations and intromissions and an increase in the number of incomplete copulations.
(2) A slight increase in the length of the series of copulations but no differences in the frequencies of intromissions. A slight decrease in the intromission per minute, especially at the end of the observation.

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(3) A steady and very regular prolongation of the refractory period takes place.

In a second experiment he analyzed the effects of pronounced sexual satiation. In this case animals were allowed to copulate *ad libitum* during one hour for five consecutive days. On the fifth day the activity was recorded. In his thesis Knut Larsson wrote:

Summarising the results of this as well as the previous investigation, we find . . . :
(1) No or only slight change in the number of intromissions preceding each ejaculation.
(2) A slight prolongation of the duration of each series of copulations, especially in the last series.
(3) A lowered number of intromissions per minute, especially at the end of the observation.
(4) Highly prolonged refractory periods.

Knut Larsson concluded that sexual satiation appears after a particular sexual behavior pattern elicited by repeated ejaculation. He carefully analyzed that pattern and found a progressive diminishing of the number of intromissions, an increase in the number of attempts (mounts), prolonged refractory periods and finally a lowering of the intensity of the reflex (intromissions per minute) as exhaustion approached. According to Knut Larsson, sexual satiation is primarily to be traced in the length of the refractory periods.

Since 1956 few research groups have studied sexual exhaustion. Different schedules have been used to develop sexual satiety and different criteria used for sexual exhaustion. However, in spite of these variations, the changes in sexual activity as sexual satiation develops, as described by Knut Larsson in his thesis, have been confirmed.

Most research groups have focused on the development rather than on the consequences of sexual satiation. Hence, Beach and Jordan (1956) considered sexual satiation as a catabolic process whose endpoint is fatigue and whose sequel is a period of recovery. Lawrence and Barfield (1975) suggested that sexual exhaustion is the result of a build-up of the refractory period that rises asymptotically as exhaustion approaches. Satiation occurs when the animal fails to re-arouse after cessation of the last active behavioral inhibition, that is, the last absolute refractory period.

In 1994 we reported on the development of sexual satiety after a particular paradigm (Rodríguez-Manzo & Fernández-Guasti, 1994). Sexually experienced male rats were allowed to mate *ad libitum* with a single receptive female and sexual behavior was recorded until a postejaculatory interval of 90 min occurred. If the rat did not copulate within this period, it was considered sexually exhausted. All animals accomplished this sexual satiation criterion within 4 hours of *ad libitum* copulation. A median number of 7 ejaculatory series was achieved before reaching the sexual exhaustion criterion; however, this number varied from 5 to 12. Analysis of sexual exhaustion development revealed that as the rat approached sexual satiation, the number of mounts did not change, while the number of intromissions decreased, the ejaculation latency tended to increase (though this did not reach statistical significance) and the postejaculatory interval increased logarithmically. In contrast to the earlier studies on sexual exhaustion, we became interested in the inhibitory period itself, once established. Thus, we found that 24 hours after the sexual satiation session, two-thirds of the exhausted animals did not show sexual behavior in the presence of a receptive female and one-third were able to execute one ejaculatory series, from which they did not recover. These proportions prevailed after increasing the observed population (to more than 100 animals), implying that sexual exhaustion can be expressed in two different ways: by the complete absence of sexual activity or by the execution of one ejaculatory series without recovery. When present, this ejaculatory series shows particular features: the intromission latency and number of mounts are increased and the number of intromissions decreased, compared with a first ejaculatory series of a rested male. But the most conspicuous feature of the sexual behavior shown by sexually exhausted rats is their inability to resume copulation after ejaculation. The involvement of physical exertion in the behavioral inhibition exhibited by the exhausted animals 24 hours after the satiation procedure was discarded, since we evaluated the spontaneous ambulatory behavior of these and control males and found no differences (Rodríguez-Manzo & Fernández-Guasti, 1994).

Once a male reaches the state of sexual exhaustion it recovers slowly. The process of recovery of sexual behavior has been little investigated. Knut Larsson in his thesis reported that, 14 days after sexual activity, the satiated animals behaved similarly to control rats (Larsson, 1956). Beach and Jordan found that a 6-day resting period was not enough for sexual recovery after satiation, but a 15-day period of sexual inactivity rendered fully rested males capable of maximal copulatory performance (Beach & Jordan, 1956). Lawrence and Barfield conducted an interesting analysis of two components of the refractory period during both the development of and recovery from sexual exhaustion. They demonstrated that, by day 6 after satiation, pre-ejaculatory measures of sexual behavior as well as the absolute refractory period had returned to baseline values, while the relative refractory period was still extended (Lawrence & Barfield, 1975).

Recently, we began to explore the recovery process of sexual activity after a 4-hour *ad libitum* copulatory session with a single female, by studying sexual behavior after various intervals in the same subjects. In the testing scheme, males were exposed to receptive females on two consecutive days after satiation (24 h and 48 h recordings) and thereafter a one-day pause was allowed (next recording at 96 h). Preliminary data show that, 48 h after the development of sexual

Table 1. *Recovery profile of sexual activity after copulation to satiation in male rats*

	Day 1	Day 2		Day 4	Day 7
		Without pause	With pause		
M	33.33%	0%	12.5%	63%	100%
I	33.33%	0%	12.5%	63%	100%
E	33.33%	0%	0%	63%	100%
CR	0%	0%	0%	63%	100%

The values represent the percentages of sexually exhausted male rats that were able to show mounts (M), intromissions (I), ejaculation (E) and to resume copulation after ejaculation (CR) at the different time intervals after the sexual exhaustion session (copulation to satiation on day O).

satiation, no animal copulated, but after 96 h 63% of the exhausted males ejaculated and resumed copulation. Seven days after satiation 100% of the subjects ejaculated and resumed copulation. The complete inhibition of sexual activity seen at the 48 h observation is, of course, influenced by both the repeated copulation during the development of sexual satiety and by the sexual activity shown by these males in the 24 h test. To discern the effects of these two factors, an independent group of animals was tested for sexual behavior 48 h but not 24 h after sexual satiety. In the latter group, 12.5% of the animals initiated sexual activity, which consisted mainly of mounts and a few intromissions without attaining ejaculation, in a 30-min period. The 96 h data reveal that, already at 4 days after copulation to exhaustion, an important percentage of the males (63%) not only exhibited ejaculation, but also recovered the capacity to resume copulation. seven days after copulation all animals were capable of executing one copulatory series. These data are shown in Table 1. Note that the return to basal values in the sexual behavior parameters seen 7 days after satiety does not imply the recovery of the ejaculatory capacity of a fully rested male, since only one copulatory series was recorded.

In relation to the ejaculatory capacity of sexually experienced male rats, several authors made an interesting observation in the early 1960s: When a male rat ceased to copulate, due to the attainment of sexual exhaustion, a change in the female partner renewed its sexual responsiveness, including the accomplishment of ejaculation (Fisher, 1962; Fowler & Whalen, 1961; Hsiao, 1969; Wilson *et al.*, 1963; Zucker & Wade, 1968). This phenomenon was named "the Coolidge effect" (Wilson *et al.*, 1963) and it was presumed to be due to an increase in sexual motivation or renewal of sexual interest based on the incentive stimulus that a new female represented to the exhausted male. Based on these data, we decided to examine the effect of a "physiological increase" in sexual motivation provided by the Coolidge effect on the sexual performance of sexually exhausted males 24 hours after the exhaustion procedure. The results revealed that the copulatory capacity of male rats is far greater than is spontaneously exhibited during a satiation session with a single female. In response to the change in the stimulus female, male rats were able to maintain copulatory activity for at least four more hours (eight hours of continuous copulation as a whole). In fact, the recording session was ended because of the termination of the dark phase of the light–dark cycle and the decrease in the females' receptivity that resulted from prolonged sexual activity. Interestingly, when these males were exposed to a receptive female the day after, 80% showed ejaculation and 50% resumed copulation after ejaculation. These data led to the conclusion that sexual motivation can preclude the establishment of the process responsible for the sexual inhibition that follows sexual satiation (Rodríguez-Manzo, 1999b).

PHARMACOLOGICAL ANALYSIS OF SEXUAL EXHAUSTION

The neurochemical examination of the satiation phenomenon was almost absent until 1987, when James Pfaus and Boris Gorzalka explored the effect of opioid antagonists on the development of sexual satiation. These authors found that naloxone retarded sexual exhaustion, since the mean time the rats spent copulating was increased but without modification of the ejaculatory capacity (Pfaus & Gorzalka, 1987). Some research groups, including our own, have studied several neurotransmitter systems: opioids (Miller & Baum, 1987; Pfaus & Gorzalka, 1987; Rodríguez-Manzo & Fernández-Guasti, 1995a; Rodríguez-Manzo *et al.*, 2002a), noradrenaline (Fernández-Guasti & Rodríguez-Manzo, 1997; Rodríguez-Manzo & Fernández-Guasti, 1994, 1995b), serotonin (Fernández-Guasti & Rodríguez-Manzo, 1997; Rodríguez-Manzo & Fernández-Guasti, 1994; Yells *et al.*, 1992), dopamine (Mas *et al.,* 1995a,b; Rodríguez-Manzo, 1999a) and GABA (Rodríguez-Manzo *et. al*., 2000). Most neurotransmitter systems seem to participate in the regulation of this interesting phenomenon via a common noradrenergic link (Rodríguez-Manzo & Fernández-Guasti, 1995b), which in turn is coupled to a dopaminergic final pathway (Rodríguez-Manzo, 1999a).

Below we review both the role of the potent 5-HT_{1A} agonist 8-OH-DPAT, and the interesting putative participation of GABA-ergic neurotransmission in sexual exhaustion. These aspects were selected because of the great importance of the contributions of Knut Larsson to both.

To recap, 24 hours after intense copulation in a sexual exhaustion session, one-third of the population showed a single ejaculation, after which they did not resume copulation, and two-thirds did not show sexual behavior at all. All the data here reported concerning our pharmacological and endocrine studies were obtained at this time.

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) has an inhibitory effect on most aspects of male sexual activity. Experimental manipulations which reduce endogenous 5-HT activity include lesions of 5-HT neurons with 5,7-dihydroxytryptamine (5,7-DHT) (Fernández-Guasti & Escalante, 1991; Larsson *et al*., 1978) or inhibition of 5-HT synthesis using p-chlorophenylalanine (pCPA) (Ahlenius *et al*., 1971; Fernández-Guasti & Escalante, 1991; Salis & Dewsbury, 1971), and these manipulations stimulate sexual activity. Furthermore, the effects of pCPA can be reversed by systemic treatment with the precursor of 5-HT, 5-hydroxytryptophan (5-HTP). Finally, the central administration of 5-HT inhibits sexual activity when injected into the medial preoptic area (mPOA) and the nucleus accumbens (Fernández-Guasti *et al*., 1992; Verma *et al*., 1989).

The finding of several serotonin receptors has raised the question of the functional link between these receptors and the mediation of the inhibitory effects of serotonin on copulatory behavior. We, together with Knut Larsson, Sven Ahlenius and Anders Agmo, proposed that the 5-HT_{1B} receptor mediates these inhibitory actions. Evidence for this proposal includes the fact that the systemic or intrabrain administration of 5-HT_{1B} agonists inhibits male sexual behavior similarly to serotonin or its precursor 5-HTP (Fernández-Guasti *et al*., 1989, 1992; Hillegaart & Ahlenius, 1998). Also, the co-administration of 5-HTP and a 5-HT_{1B} agonist, at doses that are subthreshold to inhibit male rat sexual activity, synergistically interact to inhibit this behavior (Fernández-Guasti & Rodríguez-Manzo, 1992). Additionally, selective 5-HT_{1B} receptor antagonists completely block the inhibitory effect of 5-HTP on copulation, while antagonists to other 5-HT receptor subtypes do not (Ahlenius & Larsson, 1998). The recent development of knockout mice strains with a targeted deletion of genes encoding for specific serotonin receptor proteins provides a new approach to the analysis of their role in masculine sexual behavior. Thus, in 5-HT_{1B} receptor knockout mice we found that spontaneous sexual behavior appeared to be facilitated, in the sense that the animals became interested earlier in sexual activity, although they required more stimulation to achieve ejaculation than the corresponding wild-type strain (Rodríguez-Manzo *et al*., 2002b). It has to be mentioned that in that work the inhibitory actions of serotonin on mouse sexual behavior were found to be mediated by 5-HT_{1B} receptors, but also by the 5-HT_{1A} subtype. This species difference between mice and rats makes it difficult to draw conclusions about a unique role of the 5-HT_{1B} receptor subtype in the control of masculine sexual behavior of rodents; however, the inhibitory effect of the 5-HT_{1B} receptor subtype was confirmed. Whether an increase in 5-HT_{1B} receptor number or affinity participates in the inhibition of male rat sexual behavior observed after copulation to exhaustion remains to be studied. Naturally, the introduction of new selective 5-HT_{1B} antagonists will shed light on the role of this receptor in sexual exhaustion.

In 1981, Knut Larsson and coworkers demonstrated that the administration of a then new, selective 5-HT agonist, 8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT), produced a drastic facilitation of copulatory behavior in male rats. In an extensive and detailed analysis of this effect, it was established that such facilitation was mediated by the stimulation of central 5-HT_{1A} receptors (Ahlenius *et al*., 1981). The behavioral effects of 8-OH-DPAT on masculine sexual activity (Ahlenius & Larsson, 1991) consisted primarily of a large reduction in the number of intromissions preceding ejaculation, a drastic shortening of the ejaculation latency and an increase in the percentage of sluggish animals that displayed sexual behavior.

The facilitatory actions of this drug were so clear that, in 1994, we decided to use 8-OH-DPAT as a pharmacological tool to attempt the putative reversal of sexual satiety. The initial approach of that study was to establish whether the profound inhibition of sexual behavior produced by sexual satiety could be reversed by pharmacological means. A dose of 0.25 mg/kg of 8-OH-DPAT clearly reversed the sexual inhibition characteristic of sexual exhaustion, in the sense that 24 h after satiation the animals were able to resume copulatory behavior after ejaculation and that the proportion of sexually exhausted rats showing mounts, intromissions and ejaculation was increased. Thus, 8-OH-DPAT treatment induced 90% of the animals to display sexual behavior until ejaculation, whereas around 30% of the studs did so in the control group. Furthermore, almost no control sexually exhausted males resumed copulation after ejaculating once (4%), while 71% of those treated with 8-OH-DPAT were able to reinitiate sexual activity after ejaculation (Rodríguez-Manzo & Fernández-Guasti, 1994). Interestingly, our data with 8-OH-DPAT revealed that the satiated animals responded to drug administration with the typical features described for this compound in non-exhausted animals, that is, a significant dose-dependent reduction in the number of mounts and intromissions preceding ejaculation and a drastic shortening of ejaculation latency (Ahlenius & Larsson, 1991).

In later studies we established that the integrity of the central noradrenergic system was essential for the facilitatory action of 8-OH-DPAT on the sexual activity of sexually exhausted male rats, since after its lesion the 5-HT_{1A} receptor agonist completely lost its effect (Rodríguez-Manzo & Fernández-Guasti, 1995b). Moreover, in non-exhausted male rats, neurochemical lesion of the noradrenergic system only partially blocked the facilitatory actions of 8-OH-DPAT, suggesting that sexual exhaustion contributed to completely abolish the facilitatory drug effect (Fernández-Guasti & Rodríguez-Manzo, 1997). At that time no obvious explanation for the contribution of sexual exhaustion to the cancellation of 8-OH-DPAT effects could be provided. However, recent findings on changes in androgen receptor density

in the brain provide a clue to the interpretation of these results (see below).

GABA

In 1986, we published in collaboration with Knut Larsson a series of articles on the role of the GABA-ergic system in the control of masculine sexual behavior. The main finding of those experiments was the very drastic shortening of the postejaculatory interval (and of the ultrasonic vocalization emission that characterizes this period) after the intrapreoptic injection of $GABA_A$ antagonists or inhibitors of GABA synthesis (Fernández-Guasti *et al*., 1986). These results led to the proposition that GABA serves an inhibitory role in the control of masculine sexual behavior, primarily during the postejaculatory interval. Indeed, in 1986 it was established that, after ejaculation, there is an increase of GABA levels in the cerebrospinal fluid of male rats (Qureshi & Södersten, 1986). As mentioned above, the development of sexual satiety is characterized by a progressive prolongation of the postejaculatory interval. Actually, most animals stop copulating after ejaculation. Thus, the inhibition of sexual behavior that follows copulation to exhaustion could be interpreted as a very prolonged postejaculatory interval. The data of Lawrence and Barfield showing the progressive increase in the relative refractory period as sexual exhaustion develops, together with the fact that 6 days after satiation the relative refractory period is the only sexual behavior measure that is still extended, further supported this idea (Lawrence & Barfield, 1975).

To analyze this hypothesis, we explored whether administration of the $GABA_A$ antagonist bicuculline directly into the mPOA reversed sexual exhaustion (Rodríguez-Manzo, *et al*., 2000). Although this same treatment was shown to stimulate sexual behavior by reducing the duration of the postejaculatory interval in non-satiated rats (Fernández-Guasti *et al*., 1986) it lacked effect in sexually exhausted animals. This finding revealed that a different mechanism underlies the inhibition of sexual behavior that characterizes the postejaculatory interval and the one exhibited after sexual satiation. Interestingly, a similar result was obtained after electrical stimulation of the mPOA (Rodríguez-Manzo *et al*., 2000). Thus, as previously reported (for review see Paredes in this volume) the stimulation of this brain area produces a clear facilitation of sexual behavior in non-exhausted, sexually experienced studs, but lacks an effect in sexually satiated males (Rodríguez-Manzo *et al*., 2000).

ANDROGEN RECEPTORS

It has been reported that the androgen-sensitive neurons in the mPOA participate in the regulation of copulation, since implantation of testosterone into this brain area of castrated male rats restores sexual behavior, while selective blockade of androgen receptors (AR) in this region inhibits mating (McGinnis *et al*., 1996). More direct evidence comes from recent molecular biology studies showing that mating-induced Fos expression occurs almost exclusively in AR-containing neurons located in the mPOA (Gréco *et al*., 1996, 1998).

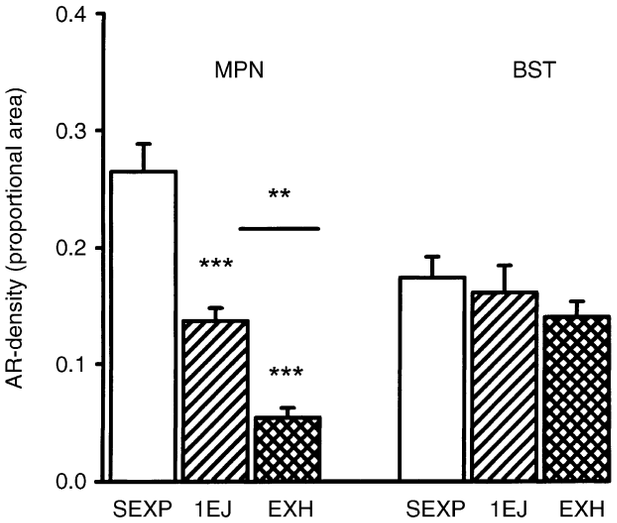

Fig. 1. Comparison of the androgen receptor (AR) density in the medial preoptic nucleus (MPN) and the bed nucleus of the stria terminalis (BST) of control sexually experienced males (SEXP) and rats that ejaculated once (1EJ) or copulated to exhaustion (EXH). Data are expressed as proportional area (i.e. the sum of the stained particle areas/evaluated area). Tukey test $^{**}p < 0.01$; $^{***}p < 0.001$.

In a recent study, we analyzed whether sexual activity altered AR immunoreactivity (Fernández-Guasti *et al*., 2003) in areas closely related to the neural and/or neuroendocrine control of sexual behavior, such as the medial preoptic nucleus (MPN) and the bed nucleus of the stria terminalis (BST) (see Meisel & Sachs, 1994). We hypothesized that changes in the androgen receptor density (ARD) could mediate the long-term alterations in sexual behavior produced by copulation. The results were compared between sexually sated rats, animals that had one ejaculation and sexually experienced subjects that had not recently copulated. The data obtained revealed a reduction in ARD in the MPN, but not in the BST. Interestingly, in the MPN this reduction was proportional to the quantity of sexual behavior displayed, since after sexual satiation fewer cells appeared marked as compared with those stained in rats that ejaculated once (see Fig. 1). These results suggest that a drastic decrease in ARD in specific brain regions might play a role in the inhibition of sexual behavior observed in sexually sated males.

Interestingly, the changes in ARD during sexual satiety could provide a key to understand a possible interaction between the function of neurotransmitter systems linked to endocrine processes. In particular, as aforementioned, 8-OH-DPAT had an action in noradrenergic-lesioned

non-sexually exhausted rats, whereas in sexually satiated animals with a noradrenergic lesion the drug completely lacked of an effect. We here propose that such difference in 8-OH-DPAT effect could be mediated, at least partially, by changes in ARD. As early as 1985, Clark and colleagues suggested that the effects of testosterone on male rat sexual behavior could be partially mediated by the noradrenergic system, since yohimbine injection stimulated mounting and intromission in long-term castrated rats (Clark *et al*., 1985). Later, Bancroft supported that proposal and extended the notion, of noradrenaline mediating androgen effects, to human sexual arousal (Bancroft, 1995). There have also been several reports suggesting that 8-OH-DPAT interacts with testosterone to stimulate male rat sexual behavior (Haensel *et al*., 1993; Mendelson & McEwen, 1990; Rowland & Houtsmuller, 1998). Finally, the interaction of 8-OH-DPAT with alpha$_2$-adrenoceptors is well documented. Taking these data together, it emerges that 8-OH-DPAT interacts with both testosterone and the noradrenergic system to exert its facilitatory actions on male rat sexual behavior, which would explain the partial and complete blockade of its effects found in sexually experienced and sexually exhausted lesioned rats, respectively. Thus, in the absence of the noradrenergic system, 8-OH-DPAT showed an attenuated facilitatory effect in sexually experienced males. However, with a concomitant lack of testosterone action, due to the sexual exhaustion-induced drastic reduction in ARD, the effects of 8-OH-DPAT were completely blocked. Naturally this proposition requires experimental support.

CONCLUDING REMARKS

Knut Larsson first described the process of sexual exhaustion, and indicated that this process develops rapidly, in terms of hours, after repeated copulation and recovers gradually during a long-term period, of several days. Interestingly, if continued stimulation is provided to the male, the sexual inhibition does not appear, suggesting that increased sexual motivation may overcome such inhibition. Using the paradigm of continuous copulation during a 4-hour period, we have found that, 24 hours later, most males show a complete inhibition of sexual behavior, while a third of the population can copulate to ejaculation, after which they do not resume copulation. The analysis of the recovery process showed a progressive increase in the proportion of males ejaculating and resuming copulation within one week after sexual exhaustion. The inhibition of sexual behavior after sexual exhaustion does not rely on motor tiredness.

In the pharmacological analysis of sexual satiety, others and we have established that various treatments, including serotonergic, dopaminergic, opioid and noradrenergic drugs, could reverse sexual exhaustion. In the action of most of these drugs, the noradrenergic and dopaminergic systems seem essential. The 5-HT$_{1B}$ receptor subtype most likely mediates the inhibitory action of serotonin on masculine sexual behavior; however, its role on sexual satiety remains to be studied. Interestingly, neither the administration of GABA antagonists nor the electrical stimulation of the mPOA reversed sexual exhaustion, leading to the conclusion that this process does not represent a very prolonged post-ejaculatory interval.

Finally, sexual behavior, and to a larger extent copulation to satiation, reduced the ARD in brain areas closely related to the expression of sexual behavior, suggesting an endocrine link in the mediation of this process. This interesting finding also opens the possibility of interactions between pharmacological and endocrine processes in the regulation of sexual satiety.

REFERENCES

Ahlenius, S., Eriksson, H., Larsson, K., Modigh, K. & Södersten, P. (1971). Mating behavior in the male rat treated with *p*-chlorophenylalanine methyl ester alone and in combination with pargiline. *Psychopharmacology*, *20*, 383–388.

Ahlenius, S. & Larsson, K. (1991). Physiological and pharmacological implications of specific effects by 5HT$_{1A}$ agonists on rat sexual behaviour. In R. J. Rodgers & S. J. Cooper (Eds.), *5-HT$_{1A}$ agonists, 5-HT$_3$ antagonists and benzodiazepines: Their comparative behavioural pharmacology* (pp. 281–315). Chichester: John Wiley & Sons.

Ahlenius, S. & Larsson, K. (1998). Evidence for the involvement of 5-HT$_{1B}$ receptors in the inhibition of male rat sexual behaviour produced by 5-HTP. *Psychopharmacology (Berlin)*, *137*, 374–382.

Ahlenius, S., Larsson, K., Svensson, L., Hjorth, S., Carlsson, A., Lindberg, P., Wikstrom, H., Sánchez, D., Arvidsson, L. E., Hacksell, U. & Nilsson, J. L. G. (1981). Effects of a new type of 5-HT receptor agonist on male rat sexual behaviour. *Pharmacology, Biochemistry and Behavior*, *15*, 785–792.

Almqvist, J. O. & Hale, E. B. (1956). An approach to the measurement of sexual behavior and semen production in dairy bulls. *Proceedings of the Congress on Animal Reproduction*, *3*, 50–59.

Bancroft, J. (1995). Are the effects of androgens on male sexuality noradrenergically mediated? Some consideration of the human. *Neuroscience and Biobehavioral Reviews*, *19*, 325–330.

Beach, F. A. & Jordan, L. (1956). Sexual exhaustion and recovery in the male rat. *Quarterly Journal of Experimental Psychology*, *8*, 121–133.

Beach, F. A. & Rabedeau, R. G. (1959). Sexual exhaustion and recovery in the male hamster. *Journal of Comparative and Physiological Psychology*, *52*, 56–66.

Bielert, C. F. & Goy, R. W. (1973). Sexual behavior of male rhesus: Effects of repeated ejaculation and partner's cycle stage. *Hormones and Behavior*, *4*, 109–122.

Bunnell, B. N., Boland, B. D. & Dewsbury, D. A. (1976). Copulatory behavior of golden hamsters *(Mesocricetus auratus)*. *Behavior*, *61*, 180–205.

Clark, J. T., Smith, E. R. & Davidson, J. M. (1985). Testosterone is not required for the enhancement of sexual motivation by yohimbine. *Physiology and Behavior*, *35*, 517–521.

Fernández-Guasti, A. & Escalante, A. (1991). Role of presynaptic serotonergic receptors on the mechanism of action of 5-HT$_{1A}$ and 5-HT$_{1B}$ agonists on masculine sexual behaviour: Physiological and pharmacological implications. *Journal of Neural Transmission (Gen. Sec.)*, *85*, 95–107.

Fernández-Guasti, A., Escalante, A. & Agmo, A. (1989). Inhibitory action of various 5-HT$_{1B}$ receptor agonists on rat masculine sexual behaviour. *Pharmacology, Biochemistry and Behavior*, *34*, 811–816.

Fernández-Guasti, A., Escalante, A., Ahlenius, S., Hillegaart, V. & Larsson, K. (1992). Stimulation of 5-HT_{1A} and 5-HT_{1B} receptors in brain regions and its effects on male rat sexual behaviour. *European Journal of Pharmacology*, *210*, 121–129.

Fernández-Guasti, A., Larsson, K. & Beyer, C. (1986). GABAergic control of masculine sexual behavior. *Pharmacology, Biochemistry and Behavior*, *24*, 1065–1070.

Fernández-Guasti, A. & Rodríguez-Manzo, G. (1992). Further evidence showing that the inhibitory action of serotonin on rat masculine sexual behavior is mediated after stimulation of 5-HT_{1B} receptors. *Pharmacology, Biochemistry and Behavior*, *42*, 529–533.

Fernández-Guasti, A. & Rodríguez-Manzo, G. (1997). 8-OH-DPAT and male rat sexual behavior: Partial blockade by noradrenergic lesion and sexual exhaustion. *Pharmacology, Biochemistry and Behavior*, *56*, 111–116.

Fernández-Guasti, A., Swaab, D. & Rodríguez-Manzo, G. (2003). Sexual behavior reduces hypothalamic androgen receptor immunoreactivity. *Psychoneuroendocrinology*, *28*, 501–512.

Fisher, A. E. (1962). Effects of stimulus variation on sexual satiation in the male rat. *Journal of Comparative and Physiological Psychology*, *55*, 614–620.

Fowler, H. & Whalen, R. E. (1961). Variation in incentive stimulus and sexual behaviour in the male rat. *Journal of Comparative and Physiological Psychology*, *54*, 68–71.

Gréco, B., Edwards, D. A., Michael, R. P. & Clancy, A. N. (1996). Androgen receptor immunoreactivity and mating-induced Fos expression in forebrain and midbrain structures in the male rat. *Neuroscience*, *75*, 161–171.

Gréco, B., Edwards, D. A., Michael, R. P. & Clancy, A. N. (1998). Androgen receptor and estrogen receptors are colocalized in male rat hypothalamic and limbic neurons that express Fos immunoreactivity induced by mating. *Neuroendocrinology*, *67*, 18–28.

Haensel, S. M., Mos, J., Van der Schoot, P. & Slob, A. K. (1993). Testosterone is required for the stimulatory effects of 8-OH-DPAT on sexual behavior in castrated male rats. *European Journal of Pharmacology*, *233*, 187–192.

Hillegaart, V. & Ahlenius, S. (1998). Facilitation and inhibition of male rat ejaculatory behaviour by the respective 5-HT_{1A} and 5-HT_{1B} receptor agonists 8-OH-DPAT and anpitroline, as evidenced by use of the corresponding new and selective receptor antagonist NAD-299 and NAS-181. *British Journal of Pharmacology*, *125*, 1733–1734.

Hsiao, S. (1969). The Coolidge effect in male rat copulatory behaviour: Failure to replicate Fisher's results. *Psychonomic Science*, *14*, 1–2.

Larsson, K. (1956). *Conditioning and sexual behaviour in the male albino rat*. Stockholm: Almqvist and Wiksell.

Larsson, K., Fuxe, K., Everitt, B. J., Holmgren, M. & Sodersten, P. (1978). Sexual behaviour in male rats after intracerebral injection of 5,7 dihydroxytryptamine. *Brain Research*, *141*, 293–303.

Lawrence, K. M. & Barfield, R. J. (1975). Differential rates of exhaustion and recovery of several parameters of male rat sexual behavior. *Journal of Comparative and Physiological Psychology*, *88*, 693–703.

Mas, M., Fumero, B., Fernández-Vera, J. R. & González-Mora, J. L. (1995a). Neurochemical correlates of sexual exhaustion and recovery as assessed by in vivo microdialysis. *Brain Research*, *675*, 13–19.

Mas, M., Fumero, B. & Pérez-Rodríguez, I. (1995b). Induction of mating behavior by apomorphine in sexually sated rats. *European Journal of Pharmacology*, *280*, 331–334.

McGinnis, M. Y., Williams, G. W. & Lumia, A. R. (1996). Inhibition of male sex behavior by androgen receptor blockade in preoptic area or hypothalamus, but not amygdala or septum. *Physiology and Behavior*, *60*, 783–789.

Meisel, R. L. & Sachs, B. D. (1994). The physiology of male sexual behavior. In E. Knobil & J. Neill (Eds.), *The physiology of reproduction* (pp. 3–105). New York: Raven Press.

Mendelson, S. D. & McEwen, B. S. (1990). Testosterone increases the concentration of ^{3}[H] 8-hydroxy-2-(di-n-propylamino)tetralin binding at 5-HT_{1A} receptors in the medial preoptic nucleus of the castrated male rat. *European Journal of Pharmacology*, *181*, 329–331.

Miller, R. L. & Baum, M. J. (1987). Naloxone inhibits mating and conditioned place preference for an estrous female in male rats soon after castration. *Pharmacology, Biochemistry and Behavior*, *26*, 781–789.

Pfaus, J. G. & Gorzalka, B. B. (1987). Opioids and sexual behavior. *Neuroscience and Biobehavioral Reviews*, *11*, 1–34.

Phoenix, Ch. H. & Chambers, K. C. (1988). Old age and sexual exhaustion in male rhesus macaques. *Physiology and Behavior*, *44*, 157–163.

Qureshi, G. A. & Södersten, P. (1986). Sexual activity alters the concentration of amino acids in cerebrospinal fluid of male rat. *Neuroscience Letters*, *70*, 374–378.

Rodríguez-Manzo, G. (1999a). Yohimbine interacts with the dopaminergic system to reverse sexual satiation: Further evidence for a role of sexual motivation in sexual exhaustion. *European Journal of Pharmacology*, *372*, 1–8.

Rodríguez-Manzo, G. (1999b). Blockade of the establishment of the sexual inhibition resulting from sexual exhaustion by the Coolidge effect. *Behavioural Brain Research*, *100*, 245–254.

Rodríguez-Manzo, G., Asai, M. & Fernández-Guasti, A. (2002a). Evidence for changes in brain enkephalin contents associated to male rat sexual activity. *Behavioural Brain Research*, *131*, 47–55.

Rodríguez-Manzo, G. & Fernández-Guasti, A. (1994). Reversal of sexual exhaustion by serotonergic and noradrenergic agents. *Behavioural Brain Research*, *62*, 127–134.

Rodríguez-Manzo, G. & Fernández-Guasti, A. (1995a). Opioid antagonists and the sexual satiation phenomenon. *Psychopharmacology (Berlin)*, *122*, 131–136.

Rodríguez-Manzo, G. & Fernández-Guasti, A. (1995b). Participation of the central noradrenergic system in the reestablishment of copulatory behaviour of sexually exhausted rats by yohimbine, naloxone, and 8-OH-DPAT. *Brain Research Bulletin*, *38*, 399–404.

Rodríguez-Manzo, G., López-Rubalcava, C., Hen, R. & Fernández-Guasti, A. (2002b). Participation of 5-HT_{1B} receptors in the inhibitory actions of serotonin on masculine sexual behaviour of mice: Pharmacological analysis in 5-HT_{1B} receptor knockout mice. *British Journal of Pharmacology*, *136*, 1127–1134.

Rodríguez-Manzo, G., Pellicer, F., Larsson, K. & Fernández-Guasti, A. (2000). Stimulation of the medial preoptic area facilitates sexual behaviour but does not reverse sexual satiation. *Behavioral Neuroscience*, *114*, 553–560.

Rowland, D. L. & Houtsmuller, E. J. (1998). 8-OH-DPAT interacts with sexual experience and testosterone to affect ejaculatory response in rats. *Pharmacology, Biochemistry and Behavior*, *60*, 143–149.

Salis, P. J. & Dewsbury, D. A. (1971). P-Chlorophenylalanine facilitates copulatory behaviour in male rats. *Nature*, *232*, 400–401.

Verma, S., Chhina, G. S., Mohan Kumar, V. & Singh, B. (1989). Inhibition of male sexual behavior by serotonin application in the medial preoptic area. *Physiology and Behavior*, *46*, 327–330.

Wilson, J. R., Kuehn, R. E. & Beach, F. A. (1963). Modification in the sexual behaviour of male rats produced by changing the stimulus female. *Journal of Comparative and Physiological Psychology*, *56*, 636–644.

Yells, D. P., Hendricks, S. E. & Prendergast, M. A. (1992). Lesions of the nucleus paragigantocellularis: Effects on mating behaviour in male rats. *Brain Research*, *596*, 73–79.

Zucker, I. & Wade, G. (1968). Sexual preferences of male rats. *Journal of Comparative and Physiological Psychology*, *66*, 816–819.