The role of adrenoceptors in the central nervous system in male and female rat sexual behavior

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Abstract

Three different phases can be distinguished in rats' sexual cycle, the introductory (precopulatory), the copulatory and the executive (ejaculatory) phases. In this review, a new analysis of existing pharmacological data is made, both in male and female rats, in which the different aspects of sexual behavior are taken into account. An effort is made to distinguish pharmacological effects on sexual behavior from a possible physiological role of noradrenaline. In addition, new data on the role of α2-adrenoceptors on female sexual behavior is presented.

The new analysis suggests that noradrenaline has a stimulatory role on the executive phase of male sexual behavior, while the introductory and copulatory phases remain unaffected. Adrenoceptors play a role in the regulation of sexual behavior in the medial preoptic area and the lateral septum. In female rats, noradrenaline also does not play a vital role in the introductory phase. Only the lordosis behavior of the copulatory phase is sometimes affected by adrenergic agents, but only under a certain hormonal condition. The medial preoptic area, the ventromedial nucleus, the arcuate ventromedial nucleus and median eminence are involved in the regulation of female sexual behavior. The new data suggest that α_2-adrenoceptors play no major role on any indices of female sexual behavior.

Contents

1. Introduction

This review was written to honor Professor Berend Olivier, an excellent scientist of the field of neuropharmacology in affective disorders. Berend has been interested in many topics in neuroscience, but studies on sexual behavior in rats always took a special place in his career.

During our latest collaboration, we were interested in the role of serotonin (5-HT) $_{1A}$ receptors in the regulation of sexual behavior and the comparison between male and female rats. At first sight, the existing literature suggests that serotonergic agents have opposite effects on male and female rat sexual behavior. 5-HT_{1A} receptor agonists, for example, facilitate sexual behavior in male rats (Ahlenius et al., 1991; Foreman et al., 1994; Haensel and Slob, 1997; Hillegaart and Ahlenius, 1998; Johansson et al., 1991; Mendelson and Gorzalka, 1986; Schnur et al., 1989), but inhibit female sexual activity (Ahlenius et al., 1986; Ahlenius et al., 1989; Fernandez-Guasti et al., 1987; Kishitake and Yamanouchi, 2003; Mendelson and Gorzalka, 1986). This seems quite conflicting, but it could simply be due to our definitions of different elements of sexual behavior. As explained in our latest reviews (Snoeren et al., 2013a, b), three different phases can be distinguished in rats' sexual cycle and if the appropriate phases of males and females are properly compared, the role of 5-HT_{1A} receptors in rats is more similar than assumed thus far.

Sexual behavior can be divided into three phases: the introductory (precopulatory), copulatory, and the executive phase (in males ejaculations, in female rats unknown) (Fig. 1). The interplay between males and females starts with behaviors like approaching and sniffing each other's anogenital regions to obtain pheromonal cues of sexual receptivity. This introductory phase is followed by the copulatory phase in which female rats in estrus display a variety of complex solicitations, also called paracopulatory (proceptive) behaviors; e.g. hopping, darting

and ear wiggling. The copulatory phase for male rats consists of repeated mounts and intromissions. In response to these copulatory behaviors, the female displays lordosis -or receptive behavior (also part of the copulatory phase)- in which the female arches her back and deflects her tail to one side allowing the male access to her vagina. After a series of mounts and intromissions, ejaculation (the executive phase) is reached, after which a post ejaculatory interval (PEI, the resting period preceding the next ejaculation cycle) of about 5 min starts. (A longer description can be found in Snoeren et al. 2013a and Snoeren et al. 2013b)

Conclusions in research on sexual behavior are often based solely on a part of the elements of the displayed male and female sexual behavior. Most often the differentiation in phases is not made. In males, for example, most conclusions in pharmacological research are based on drug effects on ejaculation, while at the same time effects on copulation are omitted. This can result in arbitrary conclusions. To give an example, a drug could decrease the ejaculation latency and meanwhile inhibit the number of mounts and intromissions. The conclusion that the drug facilitates male sexual behavior is therefore not sufficient. A better conclusion would be that the drug facilitates the behavior of the executive phase, while in the meantime it inhibits the behaviors in the copulatory phase. The same drug could, for example, also inhibit paracopulatory behaviors in females, a behavior that is part of the copulatory phase. If the first conclusion in males is maintained, this suggests that the drug has opposite effects on sexual behavior in males and females. However, if the different phases in the sexual cycle are addressed appropriately, it actually indicates that the drug has similar effects in females and in males. The different phases of the sexual cycle (introductory, copulatory and executive phases) can be regulated via different mechanisms and if addressed properly it could mean that the same mechanisms could be involved in males and females.

In this review, a new analysis of existing pharmacological data and release studies is made, both in males and females, in which the different aspects of sexual behavior are taken into account. An effort is made to distinguish pharmacological effects on sexual behavior from a possible physiological role of noradrenaline.

2. **Noradrenaline in the brain**

The noradrenaline system consists of different receptor types, including α_1, α_2, β adrenoceptors, and noradrenaline transporters. Adrenoceptors are located in the brain, spinal cord and periphery (Frankhuyzen and Mulder, 1982; Nasseri and Minneman, 1987). The receptors are localized both post- and presynaptically, as inhibitory receptors on non-adrenergic neurons (heteroceptors) and on the terminals and dendrites of the noradrenergic neurons themselves (autoreceptors) (Frankhuyzen and Mulder, 1982; Nasseri and Minneman, 1987). The α_2-adrenoceptors manifest a high level of tonic activity and their blockade markedly accelerates the synthesis and release of noradrenaline in the cortex and elsewhere (Dennis et al., 1987; Kiss et al., 1995; Millan et al., 1994). To the contrary, agonists such as dexmedetomidine result in a decrease in noradrenaline release and synthesis (Gobert et al., 1998; Millan et al., 2000). Approximately 80-90% of the released noradrenaline is taken up again through the neuronal noradrenaline transporters located at the presynaptic cell membrane (Esler et al., 1990; Schroeder and Jordan, 2012). Therefore, noradrenaline transporters play an important role in the homeostasis of the noradrenaline system.

Noradrenaline is widely distributed throughout the central and peripheral nervous system. Practically, all cell bodies of the noradrenaline neurons in the brain are localized in the pons and the medulla oblongata, as shown by lesions (Anden et al., 1966; Loizou, 1969), pharmacology

(Corrodi et al., 1970), and immunohistochemistry (Fuxe et al., 1970) experiments. The noradrenaline pathway can be divided in a ventral and dorsal pathway, in which the dorsal pathway originates from the locus coeruleus (LC) and mainly innervates the neopaleo-, meso-, and achicortex and gives rise to very fine terminal plexi (Blackstad et al., 1967; Fuxe, 1965; Maeda and Shimizu, 1972; Ungerstedt, 1971), whereas the ventral pathway (which originates in the pons and medulla oblongata) mainly innervates the hypothalamus, the preoptic area and the subcortical parts of the limbic system. The ventral pathway gives rise to fairly thick terminal plexa (Fuxe, 1965; Maeda and Shimizu, 1972; Ungerstedt, 1971). A detailed description of the distribution of noradrenaline in the rat brain and especially in the hypothalamus can be found in (Olson and Fuxe, 1972; Palkovits et al., 1974; Versteeg et al., 1976).

The involvement of specific brain regions in the different elements of male and female sexual behavior have been reviewed before (Snoeren et al., 2013a, b). There is a clear overlap between these functional brain areas and the existence of noradrenergic innervations and expression of adrenoceptors, for example in the medial preoptic area (MPOA) and the ventromedial nucleus of the hypothalamus (VMN). Lesions of noradrenaline neurons by 5-ADMP disrupt noradrenaline in MPOA and VMN and also disrupt lordosis (Davis et al., 1991). But also the nucleus paragigantocellularis (nPGI) receives a dense noradrenergic innervation from either the lateral tegmental or the locus coerulean noradrenergic cell groups (Kojima et al., 1985; Lyons et al., 1989; Rajaofetra et al., 1992). Some of the noradrenergic innervation of the spinal cord may also originate from spinal cells and play a role in motor coordination (Kjaerulff and Kiehn, 1997). It is likely that the coordinated, rhythmic contractions of the muscles involved in ejaculation are modulated by noradrenergic pathways acting on the spinal generator to release ejaculation. As suggested in (Snoeren et al., 2012a), potential candidate areas for the

noradrenergic effect on ejaculation, besides a direct effect in the spinal cord, might be the nPGI, LC and the paraventricular nucleus (PVN). α_2 adrenoceptors are widely distributed in the central nervous system (Alburges et al., 1993; Wamsley et al., 1992), and the localization of this receptor subtype in these specific brain areas have been confirmed, in addition to noradrenergic connections with other brain areas (Kojima et al., 1985; Lyons et al., 1989; Rajaofetra et al., 1992).

The existence of noradrenergic innervations and expression of adrenoceptors in brain areas that play an important role in sexual behavior confirm the involvement of noradrenaline in sexual behavior. Many pharmacological studies confirm the fact that noradrenaline is involved in male and female sexual behavior. These studies will be discussed in the next sections of this review.

3. **Noradrenaline and male rat sexual behavior**

A substantial amount of data suggests that blockade of α_2-adrenoceptors stimulates rat sexual behavior, while stimulation of this receptor inhibits copulation (Table 1). Systemic administration of clonidine, an α_2-adrenoceptor agonist, decreases the percentage of male rats that ejaculate, without affecting the number of mounts and intromissions (Clark, 1991; Clark et al., 1985). When clonidine was administered locally in the cerebral ventricles, it also decreased the percentage of rats ejaculating, but in the rats that ejaculated, it actually decreased the ejaculation latency and intercopulatory interval, without affecting other parameters of sexual behavior (Clark, 1991). In one study, systemically injected clonidine did increase the intromission latency in male rats (Clark, 1991), an effect that was also found with another α_2-adrenoceptor agonist guanabenz in sexually experienced males (Benelli et al., 1993). Systemically injected guanabenz

also increased the mount latency and postejaculatory interval, but it failed to affect the ejaculation latency (Benelli et al., 1993). Again, no effect of the α2-adrenoceptor agonist on the number of mounts was found.

This is a line with a previous study performed in our lab in which the selective α_2-adrenoceptor agonist dexmedetomidine also failed to have an effect on behaviors of the copulatory phase, and only increased the latency to ejaculation (Snoeren et al., 2012b). The role of α_2-adrenoceptors in sexual motivation was also studied in this experiment. It was found that dexmedetomidine did not affect sexual motivation. Another study showed that in contradiction to low doses, only an extreme high dose of dexmedetomidine (8 mg/kg) decreased sexual motivation (Viitamaa et al., 2006). These results were strengthened by the observation that the α_2-adrenoceptor antagonists yohimbine and atipamezole had a stimulatory effect on sexual motivation (Viitamaa et al., 2006). Though, low doses of yohimbine were ineffective on the introductory phase (Viitamaa et al., 2006).

Studies with systemically administered yohimbine, an α_2-adrenoceptor antagonist, showed stimulatory effects on the executive phase by decreasing the ejaculation latency (Clark, 1991; Clark et al., 1985; Sala et al., 1990). Yohimbine also attenuated the effects of clonidine on ejaculation (Clark et al., 1985). The effects of yohimbine on other parameters of male sexual behavior in rats are less consistent. On one hand, studies reported no effect on the latency to mount and intromission, or numbers of copulatory behaviors (Clark, 1991; Clark et al., 1985), while on the other hand a reduction in mount and intromission latencies was found (Sala et al., 1990). When the α_2-adrenoceptor antagonist yohimbine was locally injected in the cerebral ventricles, similar effects were found as a decrease in mount, intromission and ejaculation latencies (Sala et al., 1990). However, no effect was found on the number of mounts and

intromissions (Sala et al., 1990). A study in which genital anesthetization in male rats during a mating test was used showed an increase in number of mounts after yohimbine (Clark et al., 1984). Interestingly, it was also shown that the effects of yohimbine on sexual behavior (injected both systemically and in the ventricles) are dose dependent with an inverted-U shaped regression on the log of the doses (Sala et al., 1990), which might explain the differences in results. Another α_2-adrenoceptor antagonist, efaroxan, also decreased the mount and intromission latency in sexually experienced male rats, but only affected the ejaculation latency in sexually naïve males (Benelli et al., 1993). The α_2-adrenoceptor antagonist idazoxan, on the other hand, had no effect on any parameters on male sexual behavior. Only the highest dose of 10 mg/kg decreased the number of intromissions (Mos et al., 1991).

The role of α_1-adrenoceptors is much less clear. Systemic administration of methoxamine, a selective α_1-adrenoceptor agonist, at a dose of 1 and 3 mg/kg decreased the ejaculation latency without affecting other parameters of sexual activity (Clark et al., 1987). 3 Mg/kg methoxamine, however, did cause a decrease in number of intromissions, but the number of mounts was unaffected (Clark et al., 1987). The α_1-adrenoceptor antagonist prazosin, on the other hand, increased the ejaculation latency, without affecting other parameters of sexual activity in male rats (Clark et al., 1985). This suggests that the α_1-adrenoceptor plays no role in the copulatory phase, but has a stimulatory role on the executive phase of sexual behavior. Interestingly, a higher dose of methoxamine (5 mg/kg) caused an increase in mount frequency, while decreasing the number of intromissions. The latencies to first mount, intromission and ejaculation were also increased in this study (Clark et al., 1987). This suggests that methoxamine has an opposing effect at low versus high doses, but it should be mentioned that observations of gross behavioral

deficits were seen in rats treated with 10 mg/kg methoxamine (Clark et al., 1987), indicating that the importance of the effects of higher doses on copulatory behavior should be tempered. More research is needed to unravel the function of α1-adrenoceptors.

Only one laboratory explored the role of β-adrenoceptors on male rat sexual behavior. They have performed studies in which they systematically administered different β-adrenoceptor antagonists. Labetalol, a mixed α- and β-adrenoceptor antagonist, had a dose dependent effect on male sexual behavior. Only the dose of 8 mg/kg labetalol induced an increase in mount and intromissions latency. Both lower and higher doses of this agent had no effect, and also other parameters of sexual behavior remained unaffected (Smith et al., 1990). The nonspecific β-adrenoceptor antagonists pindolol and propranolol, in addition to the selective β_1-adrenoceptor antagonist atenolol, had inhibitory effect on male sexual behavior by increasing the ejaculation latency and intercopulatory interval. No effects were found in the number of mounts and intromissions or the mount and intromission latencies after injection of propranolol or atenolol (Smith et al., 1990). Only pindolol increased the number of mounts, in addition to the latency to first mount and intromission (Smith et al., 1990). One later study suggested the dose of propranolol is important for the effects on male sexual behavior, because lower doses have no effect on sexual indices besides an inhibitory effect on intromission latency (Smith et al., 1995).

Local injections of β-adrenoceptor antagonists into the cerebral ventricles showed that if β-adrenoceptors are involved, the β_2-adrenoceptor is probably involved in the inhibiting effects induced by the different β-adrenoceptor antagonists. Whereas the nonspecific β-adrenoceptor antagonists pindolol and propranolol increased the intromission and ejaculation latencies, the specific β_1-adrenoceptor antagonists atenolol and metoprolol had no effect on any parameters of

sexual behavior (Smith et al., 1996). An alternative explanation could be that interactions with the 5-HT_{1A} receptors are involved in the inhibitory effects of propranolol and pindolol (Smith et al., 1996), but this is rather speculative. In addition, it should be mentioned that a recent study showed that ventricular injections of 0.5 nmol propranolol for 6 days did not affect any parameter of sexual behavior in male rats (Thom et al., 2009). The dissimilarities in dosage and injection protocol might underlie the differences in findings.

3.1 Medial preoptic area

Some investigators studied the possible involvement of noradrenergic mechanisms locally in the MPOA (Table 1). It was found that local administration of noradrenaline in the MPOA caused a decrease in mount, intromission and ejaculation latencies. Also the intercopulatory interval and the post ejaculatory interval were decreased. In addition, noradrenaline has a stimulatory effect on number of intromissions, without affecting the number of mounts (Mallick et al., 1996). Those stimulatory effects were most likely not caused by the α_2-adrenoceptors, since the selective agonist clonidine actually increased the ejaculation latency and intercopulatory interval (Clark, 1991). However, another graph in the same study showed that the high dose of 20 nmol clonidine had actually no effect on these parameters (Clark, 1991). The low doses of clonidine injections in the MPOA also cause a reduction in number of intromissions and postejaculatory interval (Clark, 1991).

A study with an α_2-adrenoceptor antagonist injected locally in the MPOA showed that yohimbine had also no effect on male sexual behavior (Clark, 1991), but attenuated the effects of systemically administered clonidine (Clark, 1991). The α_1- and α_2-adrenoceptor antagonist phenobenzamine and the nonspecific β-adrenoceptor antagonist propranolol, on the other hand,

increased the mount, intromission and ejaculation latencies and inhibited the number of mounts and intromissions (Mallick et al., 1996), suggesting that α_1- and β-adrenoceptors are involved in the regulation of the stimulatory effects of noradrenaline on sexual behavior in the MPOA.

3.2. Lateral septum

Another brain area in which the role of adrenoceptors was studied is the lateral septum (LS) (Table 1). Studies have provided evidence for a facilitatory role of the LS in copulatory behavior, as the bilateral radiofrequency or electrolytic lesions in the LS effectively suppressed male sexual behavior (Gogate et al., 1995; Kondo et al., 1990). Similar to the effects in the MPOA, noradrenaline had a stimulatory effect on male sexual behavior when injected locally in the LS. Again, the mount, intromission and ejaculation latencies were decreased and the number of mounts and intromissions were increased (Gulia et al., 2002). This effect was probably regulated by β-adrenoceptors, because the nonspecific β-adrenoceptor agonist isoproterenol had also a stimulatory effect on ejaculation latency and number of mounts and intromissions (Gulia et al., 2002), while the antagonist propranolol inhibited these parameters in male rats injected locally in the LS (Gulia et al., 2002). The α_2-adrenoceptor antagonist yohimbine, on the other hand, showed opposite effects (Gulia et al., 2002).

3.3. Discussion

Together, these studies suggest that stimulation of the α_2-adrenoceptors inhibits and blockade stimulates the executive phase of male sexual behavior. The effect on the copulatory phase, on the other hand, seem to be rather unclear. Noradrenergic agents have an ambivalent effect on this phase, depending on the dose administered. Stimulating the α_2-adrenoceptors can

inhibit, while blocking the receptors can stimulate the copulatory phase. Also the effect of noradrenergic agents on the introductory phase appears to depend on dosage. Biphasic patterns are not unusual for drugs affecting sexual behavior. Most dopaminergic agents facilitate erections at low doses, but block them at high doses (Ferrari et al., 1986). Only high doses of α_2-adrenoceptor agonists and antagonists inhibit and stimulate, respectively, sexual motivation.

To date, the role of α_1- and β-adrenoceptors in male sexual behavior is less clear. Studies indicate that α_1-adrenoceptors play no role during the copulatory phase of male sexual behavior, because noradrenergic agents acting on this receptor do not affect mounting behavior. The executive phase of male sexual behavior, on the other hand, appears to be stimulated by α_1-adrenoceptors by decreasing the ejaculation latency. The β-adrenoceptors also play no role during the copulatory phase. Local injections of β-adrenoceptors antagonists into the cerebral ventricles showed that if β-adrenoceptors are involved, the β_2-adrenoceptor is probably involved in the inhibiting effects on the executive phase induced by the different β-adrenoceptor antagonists.

The effects of local injections of noradrenaline in the MPOA indicate that this brain area is involved in the regulation of stimulatory effect on male sexual behavior. Actually, it appears that an increase in noradrenaline in this brain area stimulates the start of the copulatory phase, in addition to the stimulatory effect on the executive phase. These effects are most likely regulated via α_1- and β-adrenoceptors and not α_2-adrenoceptors, because α_2-adrenoceptor agents are mainly ineffective on sexual behavior, while α_1- and β-adrenoceptor antagonists inhibit sexual behavior in the copulatory and executive phase.

Another brain area that regulates the stimulatory effects of noradrenaline on sexual behavior is the LS. Again, stimulatory effects were found at the onset of the copulatory and executive phase. β-Adrenoceptors seem to play an important role in this mechanism.

Unfortunately, no studies are known that investigated the role of adrenoceptors in other brain areas. As mentioned before, studies using systemically administered drugs suggest that α_2-adrenoceptors are involved in the regulation of male sexual behavior. However, the studies about the noradrenergic role on sexual behavior in the MPOA and LS suggest that α_2-adrenoceptors in those areas are less important than the α_1- and β-adrenoceptors. This suggests that α_2-adrenoceptors probably play an important role in one or more other brain areas involved in regulation of male sexual behavior. As mentioned before, potential candidate areas for a noradrenergic effect on ejaculation, besides a direct effect in the spinal cord, might be the nPGI, LC and the PVN. α_2-Adrenoceptors are widely distributed in the central nervous system and the localization of this receptor subtype in these specific brain areas and the connections with other brain areas have been confirmed. Thus, α_2-adrenoceptors might regulate ejaculation behavior in these brain areas. Hopefully, future studies will investigate this hypothesis and discover which noradrenergic mechanisms in certain brain areas are involved in the regulation of male sexual behavior.

As mentioned before, adrenoceptors also exist in the periphery (Frankhuyzen and Mulder, 1982; Nasseri and Minneman, 1987). This extensive peripheral adrenergic system is not discussed in this review, but should definitely not be forgotten. Systematically administered agents also bind to the peripheral receptors, which could cause side effects on for example the immune system (Schauenstein et al., 2000) and the cardiovascular system (Gyires et al., 2009).

Additionally, it should be mentioned that all studies presented in this review investigated the acute effects of adrenergic agents. The effects of chronic exposure to adrenergic agents, however, would be more representative for daily life, and should be included in future studies. Furthermore, an interesting focus for future experiments could be the noradrenaline transporter. This transporter plays an important role in the homeostasis of the noradrenaline system. The exact function of the transporter in sexual behavior, however, is still unknown.

4. **Noradrenaline and female rat sexual behavior**

The role of noradrenaline in female sexual behavior is not yet clear. Most studies performed in this field are studies that administer adrenoceptor agonists and antagonists locally in different brain areas. It is, therefore, difficult to determine what general effect noradrenaline has on female sexual functioning.

In our laboratory (in collaboration with Professor Dr. Anders Ågmo), we have conducted an experiment in which we investigated the role of α_2-adrenoceptors on female sexual behavior. Two selective α_2-adrenoceptor antagonists, atipamezole and yohimbine, were used in this experiment. At least two weeks before the experiment, eleven female rats were ovariectomized and subcutaneously implanted with a 5 mm long Silastic capsule (medical grade Silastic tubing, 0.0625 in. inner diameter, 0.125 in outer diameter, Degania Silicone, Degania Bet, Israel) under isoflurane anesthesia. The capsule contained 10 % 17β-estradiol in cholesterol (both from Sigma, St. Louis, MO, USA) and the ends of the capsules were sealed with medical grade adhesive silicone (Nusil Silicone Technology, Carpinteria, CA USA). The females were given progesterone (Sigma, St Louis, MO, USA) in a dose of 1 mg/rat approximately 4 h prior to testing. The steroid was dissolved in peanut oil (Apoteksproduskjon, Oslo, Norway) and injected

subcutaneously in a volume of 0.2 ml/rat. This hormonal treatment assures maximum receptivity and proceptivity (Ågmo et al. 2004).

All experiments were conducted during the dark phase of the reversed light/dark cycle. The females achieved sexual experience during another sexual behavior experiments in which they were used as stimulus females. At the drug tests, Experiment 1 and 2, the female subject was placed in a copulation cage containing a transparent plastic wall with 4 holes (4 cm diameter) that divided the cage in two compartments allowing the female to pace her sexual interactions. Five min after the female was placed in the cage, an intact male was introduced and the copulation test was started. Observation in the test lasted until the first postejaculatory intromission. The following behavioral parameters were recorded or calculated with the Observer XT software (Noldus, Wageningen, The Netherlands): the amount of time spent in each compartment, the number of crossings between the compartments, the number of paracopulatory behaviors (dart and hops), the lordosis quotient (lordosis responses/mounts and intromissions), and the received mounts and intromissions. Since there was a variation in the total time of the tests between females, the percentage of time spent with the male (time spent with the male / total time of the test * 100%) was calculated. In addition, the number of paracopulatory behaviors per time unit (paracopulatory behaviors/total time of the test) was calculated.

In Experiment 2, the effect of yohimbine on sexual incentive motivation was also investigated. Before the start of the copulation test, the female rat was placed in a sexual incentive motivation test for 10 min. The procedure of this test is described elsewhere (Snoeren et al., 2012b; Snoeren and Ågmo, 2013, 2014). A castrated male and an intact male were employed as incentives. With the help of a video tracking system (Ethovision XT, Noldus, Wageningen, The Netherlands), the time the experimental subjects spent in each incentive zone, the distance

moved during the test, the mean velocity of movement, and the time moving were measured (Ågmo, 2003; Ågmo et al., 2004). In addition, a preference score (time spent in the female incentive zone/ (time spent in the female incentive zone + time spent in the male incentive zone)) was calculated.

In Experiment 1, the female rats were injected subcutaneously with vehicle, 0.03, 0.1 or 0.3 mg/kg atipamezole 30 min before the copulation test. The females were tested once a week in a within-subject Latin Square design. In Experiment 2, the same females were injected subcutaneously with vehicle, 0.1 or 0.3 mg/kg yohimbine 20 min before the sexual incentive motivation test. After this test, the females were immediately transferred to the copulation cage for copulation testing. Again, the females were tested once a week in a within-subject Latin Square design.

For statistical analysis of the sexual incentive motivation test, the preference score and indices of ambulatory activity (distance moved, velocity and time spent moving) were evaluated with one-factor repeated measures ANOVAs. In case of significance, *a posteriori* comparisons were made with Tukey's HSD test. The time spent with the incentives was evaluated with two-factor ANOVAs for repeated measures on both factors (incentive and treatment).

Sex behavior data were analyzed with one-factor ANOVAs for repeated measures. Some of the variables were not normally distributed according to the Shapiro-Wilk test. These variables were analyzed with Friedman's one-way ANOVA. All probabilities mentioned are two-tailed.

As shown in Fig. 2, the selective α_2-adrenoceptor antagonist atipamezole had no effect on female sexual behavior. No significant differences were found on the percentage of time spent with the male or the number of crossings (Fig. 2a/b). In addition, there was no difference between vehicle and the different doses of atipamezole in the number of paracopulatory behaviors, also

not when this parameter was calculated per time unit (Fig. 2c/d). Female injected with vehicle or any dose of atipamezole showed the same lordosis quotient and received similar amounts of mounts and intromissions (Fig. 2e/f). Therefore, we can conclude that atipamezole had no effect on female rat sexual behavior.

Data analysis of Experiment 2 (with different doses of yohimbine) revealed that there was an incentive effect on time spent with the incentives ($F_{(10)}$=19.019, P<0.01). Post hoc analysis revealed that the female rat spent significantly more time with the intact male than the castrated male after all treatments in the sexual incentive motivation test (Fig. 3a). However, no drug effects and effect on interaction between treatment and incentive were found in the time spent in vicinity of the incentive.

In addition, all females showed a significant effect on preference score (Fig. 3b) when the score was compared to .5 (no preference) (Vehicle: $t_{(10)=}$2,535, P=0.03; 0.1 mg/kg yohimbine: $t_{(10)}$=3.478, P<0.01;0.3 mg/kg yohimbine: $t_{(10)}$=3.749, P<0.01). Again, no drug effects between treatments were found in the preference score.

Also the indices of ambulatory activity were investigated in this study. A significant drug effect was found in the distance moved ($F_{(20)}$=9,713, P<0.01), time spent moving ($F_{(20)}$=7,401, P<0.01), and mean velocity ($F_{(20)}$=14.775, P<0.01). Post hoc analysis revealed that the highest dose of yohimbine caused an inhibition in ambulatory activity (data not shown), indicating that yohimbine induced low levels of sedation in the females.

As shown in Fig. 4, yohimbine had no effect on female sexual behavior. No significant differences were found between the treatments on the percentage of time spent with the male or the number of crossings (Fig. 4a/b). In addition, there was no difference in the number of paracopulatory behaviors between vehicle and yohimbine, neither when this parameter was

calculated per time unit (Fig. 4c/d). Female injected with vehicle or any dose of yohimbine showed the same lordosis quotient and received similar amounts of mounts and intromissions (Fig. 4e/f).

In summary, these experiments showed that the selective α2-adrenoceptor antagonists atipamezole and yohimbine have no effect on sexual behavior in female rats. In addition, it was found in Experiment 2 that yohimbine has also no effect on sexual incentive motivation. Together, these results indicate that the α2-adrenoceptors are not involved in the regulation of sexual behavior in females during the introductory and copulatory phase.

These results are in line with another study showing that yohimbine has no effect on lordosis behavior (Davis and Kohl, 1977). Delequamine and phenoxybenzamine, another α2-adrenoceptor antagonist and nonselective adrenoceptor antagonist respectively, have also shown to be ineffective on lordosis quotient and paracopulatory behavior in ovariectomized female rats primed with both estradiol and progesterone (Davis and Kohl, 1977; Gonzalez et al., 1996). However, the same study showed that delequamine has a facilitatory effect on lordosis quotient in nonreceptive females primed with only low levels of estradiol, although no effect was found on paracopulatory behaviors (Gonzalez et al., 1996).

No other studies are available that investigated the role of adrenoceptors on female sexual motivation. However, the lack of effect of yohimbine on sexual incentive motivation was in line with a study performed in male rats. In this study, it was found that 4 mg/kg yohimbine increased sexual motivation in males, but the lower doses used in our study had also no effect in male rats (Viitamaa et al., 2006). Also the selective α_2-adrenoceptor agonist dexmedetomidine had no effect on sexual motivation in male rats (Snoeren et al., 2012a), suggesting that α_2-adrenoceptors are not involved in the introductory phase.

Our results contradict a study in female rats in which systemically administered clonidine, an α_2-adrenoceptor agonist, had no effect on lordosis behavior in ovariectomized female primed with only estradiol, but inhibited lordosis in females primed with both estradiol and progesterone (Davis and Kohl, 1977); an effect that was attenuated by co-administration of yohimbine (Davis and Kohl, 1977). The differences in results could be explained by the different method used, since the males were only allowed to mount the female 10 times. However, there is another study that has found that yohimbine actually increase lordosis behavior in female rats primed with both estradiol and progesterone (Everitt et al., 1975). Nonetheless, the dosage of yohimbine used in this study is much higher than in our experiment. The highest dose of yohimbine used in our experiment (0.3 mg/kg) already affected indices of ambivalent behavior, indicating that the dosage used by Everitt et al. must have been far too high and the effects could have been caused by other side-effects.

Together, it suggests that α_2-adrenoceptors are not involved in the introductory and copulatory phase of female sexual behavior, at least not in fully hormonally primed females. If noradrenaline is involved in the regulation of sexual behavior in females, it must involve other adrenoceptors, like the α_1- or β-adrenoceptors. A study in which a selective α1-adrenoceptor agonists (methoxamine and phenolephrine) was administered in the cerebral ventricles showed that α_1-adrenoceptor agents stimulated the lordosis quotient in ovariectomized females primed with only estradiol (Kow et al., 1992). This is in line with another study that showed that α_1-adrenoceptor antagonists injected into the ventricle attenuated the vaginal cervical stimulation-induced lordosis and paracopulatory behavior in females treated with estrogens alone (Gonzalez-Flores et al., 2007). Other adrenoceptor antagonists acting on α_2- and β-adrenoceptors had no effect on the vaginal cervical stimulation-induced sexual behavior (Gonzalez-Flores et al., 2007).

However, it has been found by others that also the β-adrenoceptor agonist isoproterenol facilitated lordosis when injected in the ventricles (Kow et al., 1992). Although, no studies are available in which the effect of systemically administered noradrenaline was investigated on female sexual behavior, studies using adrenoceptor agents suggest that noradrenaline has a facilitatory effect on the copulatory phase of female sexual behavior in terms of lordosis behavior, an effect that is probably regulated via α_1- and/or β-adrenoceptors, and definitely not via α_2-adrenoceptors. Unfortunately, all these studies were performed in ovariectomized females primed with only estrogen. Therefore, we can only conclude that α_1- and/or β-adrenoceptors are involved in sexual behavior of low hormonally primed females. All the mentioned drug effects are listed in Table 2.

4.1. Medial preoptic area

Several studies have been performed on the role of different adrenoceptors in female sexual behavior in the brain areas MPOA, VMN, arcuate-ventromedial area of the hypothalamus (ARC-VM), lateral hypothalamic area (LHA) and median eminence (ME) (Table 2). The MPOA is one of the important brain areas involved in female sexual behavior. The studies on the role of adrenoceptors in the MPOA, however, show contradictory results. On one hand, noradrenaline is thought to play an inhibitory role in the MPOA, while other studies show stimulatory effects.

It has been shown that the nonselective adrenoceptor agonists adrenaline and noradrenaline had an inhibitory effect on lordosis behavior when locally injected into the MPOA. This effect was seen in ovariectomized females primed with estradiol and progesterone (Caldwell and Clemens, 1986). This effect must have been regulated by the α_2-adrenoceptor, since clonidine also caused an inhibition in lordosis when injected into the MPOA, while phenolephrine and

methoxamine, both selective α_1-adrenoceptor agonists, and isoproterenol, a β-adrenoceptor agonist, had no effect on lordosis quotient (Caldwell and Clemens, 1986). In addition, the administration of phentolamine (α_1--adrenoceptor antagonist) and propranolol (nonspecific β-adrenoceptor antagonist) did not attenuate the inhibitory effects on noradrenaline in the MPOA (Caldwell and Clemens, 1986). Only yohimbine, an α_2-adrenoceptor antagonist, attenuated the effect of 2 µg of noradrenaline in the MPOA (Caldwell and Clemens, 1986). Local injections of the α_1-adrenoceptor antagonist prazosin in the MPOA had also no effect on lordosis behavior (Etgen, 1990), just as injection of nonspecific β-adrenoceptor antagonists pindolol and propranolol and selective β-adrenoceptor antagonist metoprolol into the MPOA (Etgen, 1990).

Therefore, it was concluded that noradrenaline has an inhibitory role in the MPOA that is probably regulated via α_2-adrenoceptors and not α_1- and/or β-adrenoceptors. Interestingly, α_2-adrenoceptor antagonists have no intrinsic effects on lordosis when locally injected into the MPOA (delequamine (Gonzalez et al., 1996); indazoxan (Etgen, 1990); yohimbine (Etgen, 1990)). This indicates that under normal basal circumstances α_2-adrenoceptors in the MPOA do not play a crucial role in sexual behavior, but with elevated levels of α_2-adrenoceptors become more important.

However, an old study by Foreman and Moss (1978) suggested another role of adrenoceptors in the MPOA. They showed that adrenaline and noradrenaline actually stimulated lordosis responses in female rats primed with low doses of estrogens (Foreman and Moss, 1978). The stimulating effects of a β-adrenoceptorsagonist seen in the same study made them suggest that the facilitation must be regulated via β-adrenoceptors, although propranolol (β-adrenoceptor antagonist) had no effect on lordosis quotient. In addition, when the females were primed with a higher dose of estrogen, isoproterenol failed to have an effect, but propranolol then inhibited

lordosis (Foreman and Moss, 1978). Peculiarly enough, the α_1-adrenoceptor agonist methoxamine inhibited lordosis behavior in the same females (primed with low and higher doses of estrogen) when injected locally into the MPOA, while the nonselective α-adrenoceptor agonist phenoxybenzamine and α_1-adrenoceptor agonist phentolamine facilitated lordosis (Foreman and Moss, 1978). Phenoxybenzamine, however, had no effect on the lordosis quotient in the females primed with higher doses of estradiol (Foreman and Moss, 1978). Overall, it was concluded that α-adrenoceptors may have a more minor role in hypothalamic control of sexual behavior mechanisms by which a masking of an inhibitory receptor may occur (Foreman and Moss, 1978).

Caldwell & Clemens (1986) argued that these differences in outcome may be explained by any of three differences in procedure and results: 1) the time of maximal effect, 2) differences in steroid treatment, and 3) the doses of noradrenaline and noradrenergic agents that were infused. The inhibitory effects of noradrenaline in the MPOA were found 5 min after administration and attenuated after 20 min (Caldwell and Clemens, 1986), while the maximal facilitatory effects were seen 105 min after infusion (Foreman and Moss, 1978). This could suggest that there is a temporally biphasic effect of noradrenaline on lordosis behavior. Another explanation for the differences was the hormone treatment. The inhibitory effects were seen in females treated with estrogen and progesterone, while the stimulatory effects were found in females with low receptivity levels. At last, the opposite effects on lordosis responses at different doses may suggest that lower doses of noradrenaline act on different adrenoceptors (possibly β-adrenoceptors), while higher doses act more immediately on the other receptors (possibly α_2-adrenoceptors) (Caldwell and Clemens, 1986).

4.2. Ventromedial nucleus of the hypothalamus

The results on the role of adrenoceptors on female sexual behavior in the VMN are also very inconclusive. Local administration of noradrenaline into the VMN turned out to stimulate lordosis behavior in ovariectomized females primed with estradiol alone (Fernandez-Guasti et al., 1985a). Also clonidine caused an increase in lordosis responses in low-primed females when injected locally into the VMN, suggesting that the α_2-adrenoceptors might be involved in this stimulatory effect (Fernandez-Guasti et al., 1985a). Interestingly, this effect was only seen 3 h after administration. Another study, on the other hand, showed that VMN injections of clonidine had no effect on lordosis behavior in estradiol-primed females (Kow et al., 1992). Local VMN injections of the α_2-adrenoceptor antagonist delequamine actually increased the lordosis quotient in ovariectomized females primed with only estradiol (Gonzalez et al., 1996), which was explained by its effect on presynaptic α_2-adrenoceptors and thereby enhancing the release of noradrenaline. In females primed with both estradiol and progesterone, it was found that the nonselective α_2-adrenoceptor antagonist idazoxan had no effect on both lordosis behavior and paracopulatory behaviors (Etgen, 1990), while the selective α_2-adrenoceptor antagonist yohimbine decreased lordosis responses without affecting the number of paracopulatory behaviors (Etgen, 1990). Etgen hypothesized that this might be caused by the different binding profiles of the antagonists. The inhibiting effects of yohimbine might reflect its significant α_1-adrenoceptor antagonist activity (Etgen, 1990). On the other hand, it was argued that both pre- and postsynaptic α_2-adrenoceptors are present in the VMN that may be affected by the antagonists but which may exert different actions on lordosis. This would then account for the inconsistent results of pharmacological manipulations of α_2-adrenoceptors (Etgen, 1990).

An additional role for α_1- and β-adrenoceptors in the VMN on female sexual behavior was suggested by studies showing that systemic co-administration of both the α_1-adrenoceptor antagonist prazosin and the nonselective β-adrenoceptor antagonist propranolol prevented the effects of locally injected noradrenaline in the VMN (Fernandez-Guasti et al., 1985a). Prazosin by itself decreased the lordosis quotient in most studies (Etgen, 1990; Fernandez-Guasti et al., 1985b; Kow et al., 1992). In one study, prazosin was ineffective, but this could be explained by the low hormonal priming in the females (Fernandez-Guasti et al., 1985b), a result that was strengthened by similar findings with the α_1-adrenoceptor antagonist phenoxybenzamine (Fernandez-Guasti et al., 1985b). Local injections of selective α_1-adrenoceptor agonists (methoxamine and phenolephrine), on the other hand, can induce lordosis behavior in females (Kow et al., 1992). The α_{1b}-adrenoceptor subtype is mainly involved in these stimulatory effects, because co-administration of the α1b-adrenoceptor antagonist cloroethylclonidine (which by itself had no effect on lordosis) attenuated the stimulatory effects of metoxamine (Kow et al., 1992).

The role of hypothalamic β-adrenoceptor in sexual behavior were strengthened by the observation that isoproterenol, an β-adrenoceptor agonist, also increased the number of lordosis responses when administered locally in the VMN (Fernandez-Guasti et al., 1985a), although this effect was also only seen 3 h after administration. Others failed to show effects by isoproterenol (Kow et al., 1992). The nonspecific β-adrenoceptor antagonists (pindolol and propanolol), on the other hand, did cause a decrease in lordosis behavior in females primed with estrogen and progesterone (Etgen, 1990; Fernandez-Guasti et al., 1985b), but not the paracopulatory behaviors (Etgen, 1990). Interestingly, the selective β_1-adrenoceptor antagonist metoprolol did not affect lordosis and paracopulatory behavior locally in the VMN (Etgen, 1990). This could indicate that

β_2-adrenoceptors are more involved in the stimulatory effects of noradrenaline rather than β_1-adrenoceptors, but this is rather speculative and should be confirmed by future experiments. Again, females treated with only estrogens were not affected by propranolol treatment in the VMN (Fernandez-Guasti et al., 1985b), suggesting that higher levels of receptivity are required for noradrenergic agents administered in the VMN in order to have an effect on sexual behavior.

4.3. Arcuate-ventromedial area of the hypothalamus

The only study performed on the role of adrenoceptors in the arcuate-ventromedial area of the hypothalamus suggests that β-adrenoceptors play a stimulatory role, while α-adrenoceptors have an inhibitory role on sexual behavior in females.

It was shown that local injections of adrenaline and noradrenaline in this brain area increased the number of lordosis responses in ovariectomized females primed with low levels of estradiol (Foreman and Moss, 1978). This effect is probably regulated via the β-adrenoceptors, because isoproterenol (β-adrenoceptor agonist) also increased lordosis, while the antagonist propranolol inhibited female sexual behavior (Foreman and Moss, 1978). It should be mentioned, though, that isoproterenol failed to have an effect on lordosis when injected in ovariectomized females primed with higher doses of estrogens (Foreman and Moss, 1978). The α_1-adrenoceptor agonist methoxamine, on the other hand, inhibited the lordosis quotient when injected locally in the ARC-VM in females primed with low or higher doses of estrogens. α_1-adrenoceptor antagonists, conversely, stimulated lordosis responses in the females (Foreman and Moss, 1978).

Since this is the only study available that investigated the role of adrenoceptors in the arcuate-ventromedial area and because the same study contradicts other studies when discussing other brain areas, it is difficult to conclude that β-adrenoceptors play a stimulatory role, while α-

adrenoceptors have an inhibitory role on sexual behavior in females. Therefore, more research is needed to clarify the role of noradrenaline in the arcuate-ventromedial nucleus. It would also be interesting to see what the more acute effects of noradrenergic agents in this brain area, whereas Foreman & Moss studied the effects after 1.75 h.

4.4. Lateral hypothalamic area

Again, there is only one study available on the role of lateral hypothalamic adrenoceptors on female sexual behavior. In this study, the effects of several α- and β-adrenoceptor agonists and antagonists were tested, but none of them affected the lordosis quotient of ovariectomized females primed with low doses of estrogens. Also adrenaline and noradrenaline turned to be ineffective when injected locally in the LHA (Foreman and Moss, 1978). Therefore, it must be concluded that adrenoceptors in the LHA are not involved in the regulation of lordosis behavior.

4.5. Median eminence

The role of adrenoceptors on female sexual behavior was also studied in the ME. Local injections of noradrenaline had a stimulatory effect on lordosis behavior in females primed with estradiol alone (Scimonelli et al., 2000). They concluded that this effect must be caused by β_1- and not α_1-adrenoceptors, since prazosin did not have an effect on lordosis responses by itself and did not attenuate the noradrenaline effects, while the β-adrenoceptor antagonists metoprolol and propranolol had no effect by themselves, but attenuated the noradrenaline effect when injected in the ME (Scimonelli et al., 2000).

4.6. Discussion

Unfortunately, there is limited amount of data available on the role of adrenoceptors in the different phases of female sexual behavior. Almost all studies have solely focused on lordosis behavior in female rats; the paracopulatory behaviors were thereby mainly excluded. In order to draw conclusions on the mechanisms behind female sexual behavior, it is important to evaluate the full spectrum of behaviors shown by females. Fortunately, more researchers nowadays focus on the effects on paracopulatory behaviors as well, besides the effects on lordosis reflexes. The function of noradrenaline and the adrenoceptors on paracopulatory behavior should be investigated more in future studies. Interestingly, besides the data shown in this review, no studies have been performed on the role of noradrenaline in female sexual motivation.

Based on the available data, we can conclude that agents acting on the adrenoceptors have no effect on paracopulatory behaviors, suggesting that noradrenaline is also not involved in the copulatory phase of female sexual behavior. However, some studies have shown that lordosis behavior can be stimulated by agents acting on the noradrenergic system. This effect is probably regulated via α_1- and β-adrenoceptor, as it has been shown that agonists acting on those receptors stimulate lordosis in rats primed with estrogens. Agents acting on α_2-adrenoceptors, on the other hand, do not affect any aspect of female sexual behavior. Unfortunately, all these studies were performed in ovariectomized females primed with only estrogens. Therefore, we can only conclude that α_1- and/or β-adrenoceptors are involved in sexual behavior of low hormonally primed females. It would be interesting to see what the effect would has been on females primed with both estrogen and progesterone. The data presented in this review showed that α_2-adrenoceptors are also not involved in the copulatory phase of fully-primed females, in addition to the introductory phase.

The role of noradrenaline and adrenoceptors in the MPOA on female sexual behavior is rather unclear. Both a stimulatory and an inhibitory function on sexual behavior have been suggested. On one hand, it was suggested that noradrenaline had a stimulatory effects on lordosis, an effect that was regulated via β-adrenoceptors. On the other hand, inhibitory effects on lordosis behavior were found when noradrenaline was injected in the MPOA. The inhibition was probably regulated via the α_2-adrenoceptors, instead of the α1- and β-adrenoceptors. These differences in results are pretty peculiar, but one important difference could be found between the studies: the stimulatory effects were again found in females treated with only estrogen, while the inhibitory effects were seen in females primed with both estrogen and progesterone. This suggests that the hormonal treatment of females is very important in the mechanisms behind noradrenergic regulation of female sexual behavior.

Another important difference was the timing in which the effects were seen. The stimulatory effect was found 3 h after drug administration, while the inhibitory effect was acute. The other studies mentioned in this review investigated mainly the acute effects of noradrenergic agents, so in comparison to those studies, it could be concluded that α_2-adrenoceptors and not the α1 and β-adrenoceptor in the MPOA play an inhibitory role on lordosis behavior.

The stimulating effect of noradrenaline could then be regulated via the ventromedial nucleus of the hypothalamus. Local noradrenaline injections in this area stimulated lordosis behavior in estrogen primed females. The role of α_2-adrenoceptors in this region is rather unclear, but α_1- and β-adrenoceptor seem to be involved in the stimulatory effects in the VMN. It has been suggested that the α_{1b}-adrenoceptor subtype and the β_2-adrenoceptor are mainly involved. Other brain areas that are involved in the noradrenergic system regulating female sexual behavior are the arcuate ventromedial nucleus of the hypothalamus and the median eminence. However, it

remains unclear via which receptors noradrenaline regulates sexual behavior in the ARC-VM. β-adrenoceptors might be involved in the stimulatory effects, while α_1-adrenoceptors might inhibit lordosis in this brain area. In the median eminence, β-adrenoceptors, and not the α_1-adrenoceptors, are involved in the stimulatory effects of noradrenaline. The lateral hypothalamus, on the other hand, is clearly not involved in the regulation of female sexual behavior.

As mentioned before, hormones play an important role in the role of noradrenaline on sexual behavior. To date, it appears that inhibitory effects can only be found in rats primed with both estrogen and progesterone, while stimulatory effects are mainly found in females primed with only estrogen. It is obvious that the hormonal status of the females is important for their sexual functioning. In addition, it has been found that levels of noradrenaline increase both in vivo (Nagle and Rosner, 1980) and in vitro (Janowsky and Davis, 1970) after injections of progesterone. Also, estrogen receptor agonists modify noradrenaline levels in the rat brain (Lubbers et al., 2010). Interestingly, estrogen modifies activity of both β- and α_1-adrenoceptors in the hypothalamus and MPOA, attenuating β-adrenoceptor swhile augmenting α_1-adrenoceptor responses (Etgen et al., 1992; Petitti et al., 1992; Ungar et al., 1993). It is tempting to speculate that attenuation of noradrenaline action at hypothalamic β-adrenoceptor along with the potentiation of noradrenaline action at the α_1-adrenoceptors are functionally related to estrogen priming of lordosis behavior. More research is needed to discover the exact relationship between hormones and noradrenaline.

Based on these observations it is clear that although lordosis and paracopulatory behaviors take place during the same phase of sexual behavior, the copulatory phase, they might be regulated via different mechanisms. A very interesting study by Hansen et al. (1980) showed

that a specific part of the ascending system of noradrenergic neurons in the brain, that is carried in the ventral noradrenergic bundle, is critically involved in the mechanisms by which tactile stimuli elicit receptivity, but not paracopulatory, behavior in the female rat (Hansen et al., 1980). It would be very interesting if this would be investigated in future.

5. General discussion

If the role of adrenoceptors in male and female sexual behavior is compared, some interesting conclusions can be made. First, α_2-adrenoceptors appears to be only involved in the executive phase of sexual behavior. Stimulation of this receptor results in an inhibition of ejaculations. In both males and females, this receptor is not involved in the introductory phase, unless extreme high doses of adrenergic agents are employed. In addition, it was found that α_2-adrenoceptors play no role in the copulatory phase in both male and female sexual behavior.

The comparison between the role of α_1- and β-adrenoceptors is interesting as well. It seems again that both receptors are not involved in the copulatory phase of sexual behavior. No effects were found on mounting behavior in males, or paracopulatory behaviors in females. However, there is proof that α_1- and β-adrenoceptors stimulate lordosis behavior in female rats. Unfortunately, these studies are performed in ovariectomized females primed with only estradiol. It is therefore not clear what the effect would have been in normal sexually active females. So it is still not possible to make a proper comparison with an intact male that shows normal sexual activity. Still, α1- and β-adrenoceptors are also involved in the executive phase, in which α1-adrenoceptors have a stimulatory and β-adrenoceptors an inhibitory role on ejaculation.

When adrenergic agents are injected locally in different brain areas, it appears that noradrenaline is also involved in the regulation of the copulatory phase in both males and

females. α_1- and β-Adrenoceptors appear to be involved in stimulating the start of the copulatory phase in male sexual behavior when injected in the MPOA and LS. In females, the same receptors stimulate lordosis behavior in VMN. Unfortunately, the data on the role of adrenoceptors in the MPOA is rather unclear. However, the stimulatory effects on lordosis were found by stimulating β-adrenoceptors in this brain region, while α_2-adrenoceptors could be involved in the inhibitory role. α_1- and β-Adrenoceptors in the MPOA and LS play also a stimulatory role in the executive phase of male sexual behavior.

Research into female sexual behavior often utilizes tests that only measure lordosis, not paracopulatory behavior. As I mentioned before, that is important to evaluate the full spectrum of behaviors in future studies. However, it should also be mentioned that the method used in most previous experiments is not sufficient to investigate the full spectrum. The experimental set-ups in the female studies use tests up to 10 mounts. This does not give the female the chance to show her full variety of sexual receptivity. In my opinion, it would be better to use a fixed time designs in future studies in order to give the females the time to show all facets of her sexual activity. This would improve the interpretation of the female sexual behavior and would also increase the possibilities to compare the results with male sexual behavior. Peculiarly enough, the test designs to explore male rat sexual behavior do provide the chance for males to show their full spectrum of sexual activity.

Overall, the comparison between males and females suggests that similar mechanisms, working via the same adrenoceptors, might be involved in the regulation of male and female sexual behavior. When the appropriate phases of sexual behavior are compared between males and females, noradrenaline appears to play a similar role in both sexes. Interestingly, noradrenaline seems to be involved in sexual behavior via different brain areas. Whereas

systemic administration of adrenergic agents turned out to have no effect on the copulatory phase, local injections in certain brain areas actually stimulated the start of this phase. More research is needed to investigate which other brain areas are involved in sexual functioning and how these brain areas communicate in order to regulate sexual behavior. But mainly we can conclude that sexual behavior in male and female rats are more similar than assumed so far.

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Fig 1. Hypothesis about the similarities between male and female rat sexual behavior.

Table 1: The effects of adrenoceptor ligands on male sexual behavior. #M = number of mounts; #I = number of intromissions; ML= mount latency; IL= intromission latency; ICI=

intercopulatory interval; EL= ejaculation latency; and PEI= postejaculatory interval; - = no effect; ↑ = stimulatory effect; ↓ = inhibitory effect; no sign = not investigated. I.C.V. = intracerebral ventricular, MPOA = medial preoptic area, LS = Lateral Septum.

Fig 2. Mean ± S.E.M. levels of sexual behavior after systemic administration of vehicle or three doses of atipamezole (0.03, 0.1 and 0.3 mg/kg) in female rats (n=11): the percentage of time spent with the male (A); the number of crossing (B); the total number of paracopulatory behaviors (C); the number of paracopulatory behaviors per time unit (D); the lordosis quotient (lordosis responses/mounts and intromissions) (E); the number of received mounts and intromissions (F).

Fig 3. Mean ± S.E.M. time in incentive zone (A) and preference score (B) after systemic administration of vehicle or two doses of yohimbine (0.1 and 0.3 mg/kg) in female rats (n=11). * Significantly different between incentives (A) or 0.5 (B), $p < 0.05$.

Fig 4. Mean ± S.E.M. levels of sexual behavior after systemic administration of vehicle or two doses of yohimbine (0.1 and 0.3 mg/kg) in female rats (n=11): the percentage of time spent with the male (A); the number of crossing (B); the total number of paracopulatory behaviors (C); the number of paracopulatory behaviors per time unit (D); the lordosis quotient (lordosis responses/mounts and intromissions) (E); the number of received mounts and intromissions (F).

Table 2: The effects of adrenoceptor ligands on female sexual behavior. LQ=lordosis quotient; OVX=ovariectomy; EB=estradiol benzoate; P=progesterone; - = no effect; ↑ = stimulatory effect;

↓ = inhibitory effect; no sign = not investigated. I.C.V. = intracerebral ventricular, MPOA = medial preoptic area, VMN = ventromedial nucleus of the hypothalamus; ARC-VM = Arcuate-ventromedial area of the hypothalamus; LHA= Lateral hypothalamic area; ME=median eminence.