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# Role of the lateral septal noradrenergic system in the elaboration of male sexual behavior in rats

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**Abstract**

The study was aimed at investigating the possible involvement of noradrenergic mechanisms in the lateral septum (LS) for elaboration of male sexual behavior in rats. In this study, norepinephrine (NE), yohimbine (YOH), isoproterenol (ISOP), propranolol (PROP), saline (SAL) and dimethyl sulfoxide (DMSO) were injected bilaterally in the LS in six different groups of sexually active male rats, and various components of sex behavior were recorded. The application of NE (3 μg) and $\alpha_2$-antagonist YOH (1 μg) produced a stimulation of most of the components of male sexual behavior, and there was increase in sexual arousal as well as performance. The microinfusion of nonspecific β-agonist ISOP (2 μg) also produced a stimulation of copulatory behavior whereas β-antagonist PROP (2 μg) produced an inhibition. The stimulation of male sexual behavior by YOH application at the LS could be due to an increased release of NE by its blocking effect on presynaptic $\alpha_2$-receptors. These results suggest that the noradrenergic system in the LS has stimulatory effect upon male sexual behavior, probably acting through β-receptors. © 2002 Elsevier Science Inc. All rights reserved.

*Keywords:* Lateral septum; Sexual behavior; Norepinephrine; Propranolol; Isoproterenol; Yohimbine

## 1. Introduction

The septum is a nodal structure in the forebrain, which links the medial preoptic area (mPOA), amygdala and hippocampus (DeFrance, 1976; Swanson and Cowan, 1979). This area has been suggested to have a role in mediating male sexual behavior besides influencing a variety of other motivational and emotional functions (Baum et al., 1982; Gogate et al., 1995; Kondo et al., 1990; Kumar et al., 1996; MacLean and Ploong, 1962; Michal, 1973). Recent studies have provided evidence for its facilitatory role in copulatory behavior, as the bilateral radiofrequency or electrolytic lesions in lateral septum (LS) effectively suppressed male sexual behavior (Gogate et al., 1995; Kondo et al., 1990). *N*-methyl-D-aspartic acid lesion of the septum, along with mPOA, also produced a complete abolition of male sexual behavior (Kumar et al., 1996).

The septum is richly innervated by noradrenergic fibers arising from the locus coeruleus and caudal brain stem (Moore, 1978; Swanson and Hartman, 1975). Norepinephrine (NE) is believed to play a facilitatory role in the central regulation of male sexual behavior in rats (Bitran and Hull, 1987; Dhawan et al., 1996; Mallick et al., 1996; McIntosh and Barfield, 1984). However, the role of the noradrenergic system in the LS, in altering the male sexual behavior, is not well understood. The present study is aimed at finding out the changes in male sexual behavior in rats after application of one selected dose of some noradrenergic agonists and antagonists at the LS.

## 2. Materials and methods

### 2.1. Animals and surgical procedures

Adult male Wistar rats, weighing 180–250 g, were used in the study. The animals were kept in controlled temperature (25 ± 2 °C) under 14:10 h light–dark schedule (lights on at 6:00 a.m.). Food and water were provided ad libitum. The rats were screened for sexual behavior and those having a sex drive score (SDS) above five were chosen for the study. Under sodium pentobarbital anesthesia (40 mg/kg body weight ip), 26-gauge bilateral guide cannulae with indwelling styli were implanted in the brain, 1 mm above the

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LS, at the coordinates 7.8 mm anterior, 0.75 mm lateral and 2.75 mm above the interaural zero, as per DeGroot's (1959) atlas. The whole assembly was firmly fixed to the skull with four implanted anchoring screws and dental cement.

### 2.2. Behavioral test details

Seven days after the implantation of the cannulae, the rats were tested for their copulatory activity using standard criteria (Mittimohan et al., 1989) on three occasions, at an interval of 3 days between the tests to observe consistency in behavior. Sex behavior scoring was performed under dim illumination in a wooden box ($45 \times 30 \times 30$ cm) with a sliding glass front, during the dark phase of the light–dark cycle (8:00–11:00 p.m.). Bilaterally ovariectomized females of the same strain, primed with 25 μg of estradiol benzoate and 1 mg of progesterone, were used as receptive partners. The male rat was introduced into the test arena 5 min prior to introduction of the female, and recording was initiated at the entry of the female into the box. A computer program was used to record the latencies of pursuit (PL), mount (ML), intromission (IL) and ejaculation (EL), frequencies of pursuit (PF), mount (MF), intromission (IF), intervals of postejaculation (PEI) and mean inter–intromission (MIII) and SDS in these rats. The software used features a method of quantifying sexual behavior using an IBM-compatible PC (Mallick et al., 1993). The latencies and frequencies of events (pursuit, mount, intromission and ejaculation) were registered by pressing the assigned keys manually. The computer did timing operation by using its internal clock. The timed parameters of copulatory activity and SDS were processed by the computer to a give a printout of the result at the end of the recording. For the purpose of quantification, weightage was given to different components of male sexual behavior. Pursuit, pursuit plus mount, pursuit plus intromission and pursuit plus ejaculation were given scores 1, 2, 3 and 4, respectively, as they were considered to indicate increasing degrees of sex drive. The weighted counts of all events were added up and divided by the test period in minutes to get the SDS. The test was terminated if the ML or IL exceeded 15 min or EL more than 30 min. Mean of 3 days recording of various parameters of male sexual behavior was taken as control reading for comparison with posttreatment values.

### 2.3. Drugs

The study was conducted on 43 rats. Seven rats were used for pilot study and the remaining 36 were divided into six groups with six animals in each group. The nonspecific effect of vehicle infusion was tested using two groups, i.e., saline (SAL) and dimethyl sulfoxide (DMSO). NE (arterenol bitartrate), $\alpha_2$-antagonist yohimbine (YOH), nonspecific β-agonist isoproterenol (ISOP) and β-antagonist propranolol (PROP) were injected in the LS in four different groups of rats, at the doses mentioned in Tables 1 and 2. All the drugs were dissolved in SAL, except YOH, which was dissolved in 25% DMSO. These drugs were procured from Sigma Chemicals, USA, The drug or vehicle was infused bilaterally in small volumes (0.2 μl) by a slow injector at the rate of 0.1 μl /min. The injector cannula was left in place for 1 min following injection. The cannula was then replaced with the stylus. The injection was given only once in any one brain site in each of the animals (Routtenberg, 1972). The sex scoring started after 10 min of administration of the drug.

The selection of drug dose was based either on the results obtained from pilot studies or on the available literature.

Table 1
The latencies and intervals (mean and S.D.) of various components of male sexual behavior of six groups of animals before (C) and after infusion of drugs (A)

| | | C | | | | | | A | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | | PL$^+$ | ML | IL$^+$ | EL$^+$ | PEI$^+$ | MIII | PL | ML | IL | EL | PEL | MIII |
| SAL (0.2 μl) | Mean | 0.05 | 0.09 | 0.14 | 5.76 | 6.48 | 0.53 | 0.04 | 0.09 | 0.18 | 5.97 | 6.52 | 0.57 |
| | S.D. | 0.04 | 0.07 | 0.12 | 3.28 | 1.48 | 0.24 | 0.03 | 0.07 | 0.13 | 3.28 | 0.49 | 0.24 |
| NE (3.0 μg) | Mean | 0.14 | 0.27 | 1.36 | 12.86 | 6.89 | 0.69 | 0.04* | 0.08* | 0.20*,# | 9.78*,# | 4.63* | 0.48* |
| | S.D | 0.14 | 0.22 | 1.70 | 2.70 | 2.20 | 0.25 | 0.02 | 0.05 | 0.21 | 2.54 | 1.61 | 0.23 |
| ISOP (2.0 μg) | Mean | 0.05 | 0.15 | 0.79 | 12.33 | 7.70 | 0.61 | 0.03* | 0.10 | 0.83 | 7.54*,# | 7.29 | 0.37* |
| | S.D. | 0.01 | 0.08 | 1.07 | 3.64 | 1.81 | 0.17 | 0.01 | 0.07 | 1.52 | 3.56 | 4.04 | 0.15 |
| PROP (2.0 μg) | Mean | 0.05 | 0.14 | 0.23 | 7.77 | 4.80 | 0.38 | 0.09* | 0.22 | 0.31 | 13.9* | 6.42* | 0.65* |
| | S.D. | 0.04 | 0.11 | 0.21 | 2.59 | 0.71 | 0.15 | 0.05 | 0.20 | 0.18 | 3.64 | 1.45 | 0.24 |
| DMSO (0.2 μl) | Mean | 0.03 | 0.31 | 0.45 | 9.18 | 7.90 | 0.66 | 0.02 | 0.27 | 0.32* | 6.97* | 7.47 | 0.56 |
| | S.D. | 0.01 | 0.37 | 0.50 | 4.64 | 1.01 | 0.26 | 0.01 | 0.31 | 0.37 | 3.00 | 0.68 | 0.15 |
| YOH (1.0 μg) | Mean | 0.08 | 0.25 | 0.91 | 10.54 | 7.10 | 0.63 | 0.03*,# | 0.11 | 0.14* | 4.62* | 5.58* | 0.33* |
| | S.D. | 0.07 | 0.21 | 0.58 | 4.87 | 1.17 | 0.16 | 0.01 | 0.08 | 0.06 | 2.25 | 1.61 | 0.12 |

The parameters showing significant differences in before-injection values (C) in group comparison, using Kruskal–Wallis ANOVA, are indicated with the superscript +. Latencies and intervals (in minutes) after the drug treatment (A) were compared with the scores before drug treatment (C). The difference between the pre- and posttreatment was taken for comparison for those parameters (PL, IL, EL and PEI) that showed significant difference in control values, whereas actual scores were taken for comparison with other parameters (ML and MIII) that did not show significant difference before injection.
The NE, ISOP and PROP groups were compared with SAL, and YOH with DMSO. $n = 6$.

* $P < .05$, significantly different after treatment compared to control.

\# $P < .05$, significance of comparison of drug with vehicle.

Table 2
The frequency (mean ± S.D.) of occurrence of different components of male sexual behavior of six groups of animals before (C) and after infusion of drugs (A)

| | | C | | | A | | |
|---|---|---|---|---|---|---|---|
| Drug | | $PF^+$ | MF | $IF^+$ | PF | MF | IF |
| SAL (0.2 μl) | Mean | 5.58 | 4.08 | 11.75 | 6.67 | 3.67 | 11.67 |
| | S.D. | 3.04 | 1.40 | 5.78 | 2.67 | 1.67 | 6.34 |
| NE (3.0 μg) | Mean | 5.69 | 3.42 | 9.65 | 10.86*,# | 6.11*,# | 14.45# |
| | S.D. | 1.67 | 1.47 | 3.50 | 3.97 | 2.74 | 7.62 |
| ISOP (2.0 μg) | Mean | 7.96 | 4.23 | 11.18 | 10.08 | 8.09*,## | 13.95*,# |
| | S.D. | 1.72 | 1.26 | 4.06 | 3.76 | 2.87 | 3.09 |
| PROP (2.0 μg) | Mean | 8.41 | 4.60 | 16.87 | 4.61*,# | 3.40* | 11.81*,# |
| | S.D. | 3.53 | 2.42 | 4.20 | 2.23 | 1.43 | 3.32 |
| DMSO (0.2 μl) | Mean | 4.25 | 4.38 | 7.91 | 4.45 | 2.86 | 8.02 |
| | S.D. | 1.24 | 1.43 | 1.45 | 1.26 | 0.63 | 1.10 |
| YOH (1.0 μg) | Mean | 7.07 | 4.49 | 8.96 | 13.03*,# | 9.47*,## | 14.89*,# |
| | S.D. | 1.19 | 1.30 | 1.46 | 1.87 | 4.75 | 2.54 |

The parameters showing significant differences in before-injection values (C) in group comparison, using Kruskal–Wallis ANOVA, are indicated with the superscript +. Frequencies after the drug treatment (A) were compared with the scores before drug treatment (C). All the frequencies were expressed as number of events per 10 min. The difference between the pre- and posttreatment is taken for comparison for those parameters (PF and IF) that showed significant difference in control values, whereas actual scores were taken for comparison of MF, which did not show significant difference before injection.
The NE, ISOP and PROP readings were compared with SAL, and YOH with DMSO. $n = 6$.

* $P < .05$, significantly different after treatment compared to control.

\# $P < .05$, significance of comparison of drug with vehicle.

\#\# $P < .01$, significance of comparison of drug with vehicle.

Bilateral injection of 1 μg of PROP in the LS in rats ($n = 4$) produced increase in PEI from 4.27 ± 1.28 to 6.43 ± 4.40 min and EL from 11.15 ± 3.71 to 12.07 ± 6.64 min and a marginal decrease in SDS (6.23 ± 2.15 to 6.09 ± 2.78). Though the inhibitory trend was evident even in the 1-μg dose, bilateral injection of 2 μg PROP significantly influenced most of the components of sex behavior. Thus, 2 μg PROP was used in this study. The injection of 4 μg ISOP ($n = 3$) produced motor deficits in animals. Therefore, a 2-μg dose was used. A dose of 1 μg was considered appropriate for YOH, as higher doses have inverted-U effect (stimulating/depressing) on sex behavior (Sala et al., 1990). NE was used at the dose of 3 μg as it has been shown to be the effective dose for inducing changes on male sexual behavior, when applied at the adjoining area, i.e., the mPOA (Mallick et al., 1996).

At the end of the experiment, the brain sites and the spread of injection were verified histologically by injecting 0.2 μl of 2% ferric chloride through the implanted guide cannulae, and then perfusing the brain with 10% formalin saline containing 3% potassium ferrocyanide (Bagga et al., 1981). The experiments were performed in accordance with the guidelines laid by the Animal Ethics Committee of the All India Institute of Medical Sciences, New Delhi, India.

### 2.4. Data analysis

To find out the variation among the three control readings, nonparametric two-way analysis of variance (Friedman ANOVA) was done for all the parameters of sex behavior in each group. Studies were done only on those rats where there was no significant variation among the three control scores. The mean of these three values for each rat was taken for comparison with the postinjection values.

Preinjection parameters were analyzed using Kruskal–Wallis nonparametric ANOVA. The effects of drug treatment were analyzed by comparing control readings with postinjection scores using Wilcoxon matched-pairs signed-ranks test (Fig. 1, Tables 1 and 2). The difference between pre- and posttreatment was taken for those parameters that showed significant difference in control readings, in-group comparison using Kruskal–Wallis ANOVA test. The groups that showed significant difference and the level of significance were found out by using multiple-range test (Fig. 1, Tables 1 and 2).

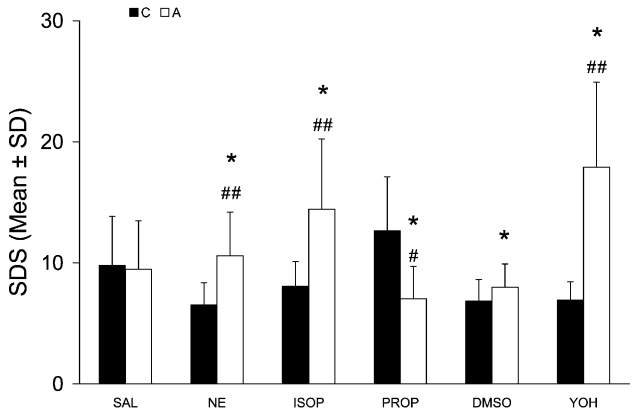


Fig. 1. Sex drive score (SDS) before drug treatment (C), and after the drug treatment (A). *$P < .05$, significantly different after treatment, compared to before treatment. The significance of difference on SDS after NE, ISOP and PROP administration when compared to SAL, and YOH when compared to DMSO is shown by $^{\#}P < .05$, $^{\#\#}P < .01$. $n = 6$. The difference between the pre- and posttreatment is taken for comparison as control values showed significant difference in Kruskal–Wallis ANOVA.

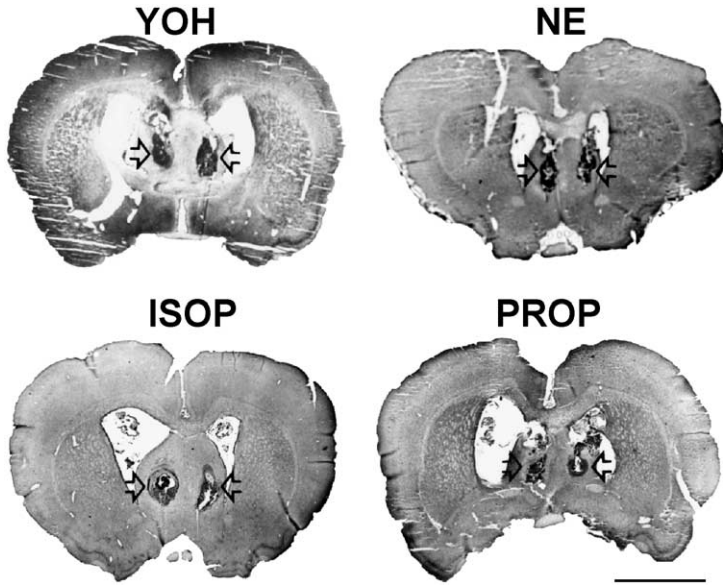


Fig. 2. The photomicrograph showing four representative brain sections from animals, which received YOH, NE, ISOP and PROP injection at the LS. The area of the brain that was stained by ferric chloride, indicating the site of injection and spread of drug, is shown by arrows. Scale bar = 4 mm.

Readings of NE, ISOP and PROP with SAL and that of YOH with DMSO were compared using Kruskal–Wallis ANOVA test to find out the effect of drug treatment compared to that of vehicle.

## 3. Results

The three postoperative control recordings, taken on three different days, in each of the six groups of rats, showed no significant variation [$F(2,18) = 2.33$, $P > .20$] on any of the components of male sexual behavior as revealed by ANOVA. On these animals that showed consistent sex behavior, the drugs, including SAL and DMSO, were tested. The injection of SAL in the LS did not produce any significant effect on any of the parameters of the sexual behavior (Fig. 1, Tables 1 and 2). The injection of DMSO produced significant decrease in MF, IL and EL, and an increase in SDS. There was no significant effect on other parameters (Fig. 1, Tables 1 and 2). Administration of NE produced a decrease in all the latencies and intervals when compared with pretreatment control (Table 1). There was increase in PF, MF and SDS after NE treatment (Fig. 1, Table 2). The effect of NE treatment when compared with the SAL group, showed significant decrease in IL and EL (Table 1). There was significant increase in SDS and all the frequencies (Fig. 1, Table 2). The comparison of reading after YOH infusion with their own pretreatment control showed significant decrease in PL, IL, EL and all the intervals, and increase in SDS and all the frequencies (Fig. 1,

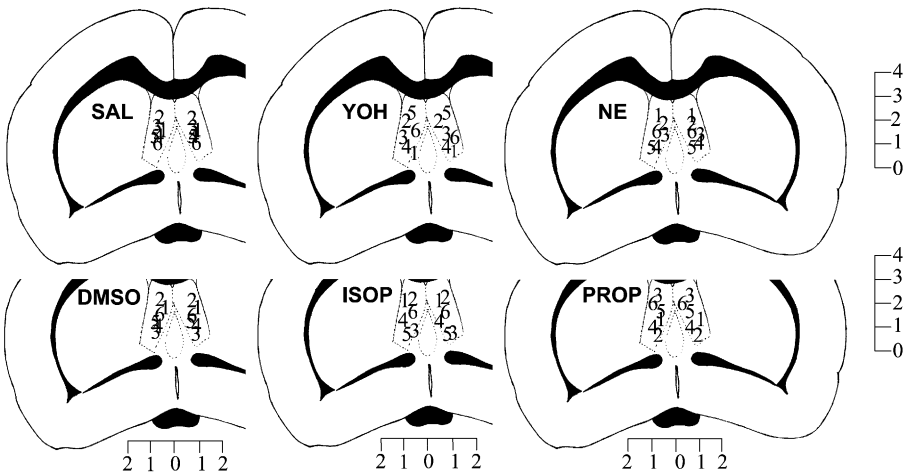


Fig. 3. The sites of injection of SAL, DMSO, YOH, NE, ISOP and PROP in different groups of animals. The numbers 1–6 represent the central point of drug injection in six different animals each, in six different groups. The sites of drug injection were reconstructed from histological sections and drawn at the coordinate of A 7.8 as per DeGroot's (1959) atlas.

Tables 1 and 2). The comparison of YOH treatment with the DMSO group showed that it produced a decrease in PL (Table 1). There was significant increase in SDS and all the frequencies (Fig. 1, Table 2). ISOP produced a significant increase in MF, IF and SDS when compared with pretreatment control and SAL (Fig. 1, Tables 1 and 2). There was significant decrease in PL, EL and MIII on comparison with control, but the decrease was significant in EL only, when compared with the SAL group. There was a significant reduction in SDS after PROP administration when compared to preinjection and also SAL control (Fig. 1). This drug produced a significant decrease in all frequencies and an increase in all intervals when compared with preinjection control. Of all the latencies, there was significant increase for PL and EL (Table 1). PROP produced significant decrease in PF and IF when compared with SAL group. Though locomotor activity was not quantified with any recording device, no motor deficit was observed, and the animals spent more time in self-grooming.

The spread of the drug, inferred indirectly on the basis of spread of the stain, was largely confined to the LS (Fig. 2). The injection sites of drugs are depicted in Fig. 3. The histological sections showed bilateral Prussian-blue-stained areas and these were mostly elliptical in shape, with their long axis extending along the injector cannulae. In some animals, it slightly extended to the adjoining areas like the bed nucleus of proprius commissurae anterioris, nucleus accumbens septi and bed nucleus of stria terminalis.

## 4. Discussion

The results of the study showed that increasing the NE content at the LS by administration of NE or YOH facilitated most of the components of male sexual behavior. The nonspecific β-agonist ISOP caused stimulation whereas β-blocker PROP produced an inhibition of male sexual behavior.

The effect of application of agonists and antagonists of NE in the LS on different components of male sexual behavior has not been reported earlier. A decrease in the initiation latencies to copulation, i.e., PL, ML, IL and PEI, on application of NE and PL, IL and PEI on injection of YOH compared to control, indicate an increase in the sexual arousal (Beach, 1956). Some of these parameters like IL after NE and PL after YOH were also significantly decreased when compared to vehicle injection. There was also an improvement in the sexual performance, as indicated by a significant rise in the SDS, as compared to control and vehicle injection. Reduction in MIII and EL after NE and YOH, compared to control injection, further substantiates this contention (Beach, 1956). Decrease in EL after NE injection was also significant when compared to SAL injection.

DMSO was used as a vehicle for administration of YOH. Decrease in IL, EL and increase in SDS after DMSO administration could be taken to indicate a stimulation in male sex drive. But a simultaneous decrease in MF, on the other hand, would indicate an opposite trend. Thus, it is difficult to explain the results obtained after DMSO injection. The facilitatory effect observed on YOH administration was found to be significant, on comparison with preinjection control readings. Most of the components like PL, SDS and all the frequencies were significantly altered after YOH injection when compared to DMSO injection. The facilitatory effect of YOH on the sexual behavior was probably brought about by its blocking action on $\alpha_2$-adrenergic presynaptic receptors, resulting in the increased availability of NE for its postsynaptic action (Ueda et al., 1983). Increasing the availability of NE at the LS, either by local application of NE itself, or by applying YOH, produced sexual arousal and improved copulatory performance.

Systemic administration of adrenergic agents have been shown to facilitate sexual behavior. NE synthesis inhibitor diethyldithiocarbamate, when applied systemically, caused a significant lengthening of the postejaculatory refractory period and IL (McIntosh and Barfield, 1984). YOH is known to have aphrodisiac properties. Systemic administration of YOH is known to produce sexual motivation in male rats as evidenced by increased mounting performance in both ex copula and in copula paradigms (Clark et al., 1984, 1985; Sala et al., 1990), whereas injection of clonidine depressed male copulatory behavior (Clark, 1991). These systemic administration studies show that the $\alpha_2$-adrenoreceptors can exert an inhibitory influence on sexual motivation. YOH is suggested to induce sexual motivation by its action on the central nervous system (Sala et al., 1990). It was also suggested that increased noradrenergic tone facilitates many aspects of male copulatory behavior whereas a reduction in noradrenergic tone inhibits such behavior (Clark et al., 1984, 1985; McIntosh and Barfield, 1984; Rodriguez-Manzo and Fernandez-Guasti, 1995; Smith and Davidson, 1990). It is possible that the changes in sexual behavior in the above-mentioned studies might have been brought about by its action at the LS. The changes produced by adrenergic agents at the LS are similar to the effect of NE application in the mPOA (Mallick et al., 1996). It is possible that the noradrenergic neuronal circuitry involved in the elicitation of male sexual behavior is spread over both the LS and the mPOA, as the lesion in the septum and the mPOA produce more drastic inhibition of mating behavior as compared to lesion in the mPOA alone (Kumar et al., 1996). The septo-preoptic region has also been shown to be important for penile erection (MacLean and Ploong, 1962). Recent reports have shown induction of immediate early genes such as c-Fos in the LS and the POA following sexual stimulation and behavior (Pfaus and Heeb, 1997).

Local injection of adrenergic agents at the mPOA has shown that it is the β-noradrenergic system that is primarily involved in the elaboration of male sexual behavior (Mallick et al., 1996). ISOP, a nonspecific agonist, and PROP, an antagonist, were administered at the LS in this study to find

out the involvement of β-receptors. The application of ISOP at the LS produced a reduction in PL, EL, MIII and an increase in SDS. The increase in SDS, MF and IF and decrease in EL were significant even when compared to SAL injection. The administration of PROP generally produced an opposite effect resulting in inhibition of male sexual behavior. There was a decrease in sexual arousal as well as reduced sexual performance by the application of PROP. The results emphasize the role of β-receptors in the LS in the modulation of sexual behavior. The systemic injection of PROP suppressed copulatory behavior (Malmnas, 1973), produced erectile difficulties (Burnett and Chaine, 1979; Kostis et al., 1990) and impaired libido (Von Arsadalen and Wein, 1982) in hypertensive patients. The intraperitoneal injection of clenbuterol, a partial β-adrenoceptor agonist with high selectivity for $\beta_2$-receptors, improved copulatory performance of sexually sluggish rats (Benelli et al., 1990). The subcutaneous injection of PROP is known to produce inhibition of both sexual motivation and performance, and genital reflexes, but the precise mechanism through which PROP induced the sexual dysfunction in such studies is not clear (Smith et al., 1995). The central action of nonspecific β-blocker PROP may be due to simultaneous blockade of both $\beta_1$- and $\beta_2$-adrenoreceptors, as either intracerebroventricular administration of $\beta_1$-antagonist or subcutaneous administration of $\beta_2$-antagonist alone, produced no major changes in copulatory behavior (Smith et al., 1996).

It may be noted that the control SDS was higher in PROP-injected group. Though the rats were grouped by random selection, some minor contribution of higher control value on the results cannot be totally ruled out.

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