

Lateral Hypothalamic Serotonin Inhibits Nucleus Accumbens Dopamine: Implications for Sexual Satiety

Daniel S. Lorrain, Jon V. Riolo, Leslie Matuszewich, and Elaine M. Hull

Department of Psychology, State University of New York at Buffalo, Buffalo, New York 14260

Dopamine (DA) is released in several brain areas, including the nucleus accumbens (NAcc), before and during copulation in male rats. DA agonists administered into this area facilitate, and DA antagonists inhibit, numerous motivated behaviors, including male sexual behavior. Serotonin (5-HT) is generally inhibitory to male sexual behavior. We reported previously that 5-HT is released in the anterior lateral hypothalamic area (LHA_A) and that a selective serotonin reuptake inhibitor microinjected into that area delayed and slowed copulation. Our present results, using high temporal resolution microdialysis, (1) confirm previous electrochemical evidence that extracellular levels of DA increase in the NAcc during copulation and decrease during the

postejaculatory interval (PEI) and (2) reveal that LHA_A 5-HT can inhibit both basal and female-elicited DA release in the NAcc. These findings suggest that the neural circuit promoting sexual quiescence during the PEI includes serotonergic input to the LHA_A, which in turn inhibits DA release in the NAcc. These findings may also provide insights concerning the inhibitory control of other motivated behaviors activated by the NAcc and may have relevance for understanding the sexual side effects common to antidepressant medications.

Key words: serotonin; lateral hypothalamic area; dopamine; nucleus accumbens; copulation; postejaculatory interval; microdialysis; male rats

Male sexual behavior in humans, nonhuman primates, and rodents is influenced by dopamine (DA) and serotonin (5-HT) neurotransmission (Bitran and Hull, 1987; Gorzalka et al., 1990; Zajecka et al., 1991; Meston and Gorzalka, 1992; Wilson, 1994; Melis and Argiolas, 1995). In general, DA enhances, whereas 5-HT inhibits, sexual motivation and performance and thus may contribute to initiation and satiety, respectively.

In the presence of sexually relevant stimuli, extracellular DA increases in the nucleus accumbens (NAcc) (Mas et al., 1990; Pfaus et al., 1990; Damsma et al., 1992; Fiorino et al., 1997) and the medial preoptic area (MPOA) (Hull et al., 1995) of male rats; DA levels increase further during copulation. DA remains elevated until the male ejaculates, after which DA levels decrease (Blackburn et al., 1992). After a postejaculatory interval (PEI) of sexual refractoriness, copulation resumes and is paralleled by enhanced DA release. This pattern has helped define a role for DA in facilitating male sexual behaviors. However, factors that inhibit DA release after ejaculation (and thus may contribute to the PEI) have received little attention.

Serotonin generally inhibits copulation. Sexual behavior is impaired by many 5-HT agonists and agents that increase 5-HT availability and is facilitated by serotonergic lesions and many receptor antagonists (Bitran and Hull, 1987; Gorzalka et al., 1990; Wilson, 1994). These experiments foster the hypothesis that endogenous 5-HT may be released at ejaculation and may regulate the PEI. *Ex vivo* preoptic tissue levels of 5-HT (Mas et al.,

1987) and *in vivo* preoptic microdialysate measures of 5-hydroxyindoleacetic acid [the main metabolite of 5-HT (Fumero et al., 1994)] increased significantly only after ejaculation. Thus, 5-HT may be released in serotonergic terminal fields, including the preoptic area, and promote sexual refractoriness during the PEI. We recently measured extracellular 5-HT in the MPOA but found no changes during copulation or after ejaculation (Lorrain et al., 1997). Extracellular 5-HT did, however, increase in the nearby anterior lateral hypothalamic area (LHA_A) immediately after ejaculation. 5-HT in the LHA_A subsequently decreased to near baseline levels before copulation resumed. Furthermore, microinjection of a selective serotonin reuptake inhibitor (SSRI) into the LHA_A delayed the onset of copulation (similarly to the PEI) and delayed ejaculation after the male resumed copulation (Lorrain et al., 1997). Clearly, 5-HT release in the LHA_A is inhibitory to copulation and may contribute to the PEI.

5-HT projections originating in the raphe may suppress forebrain catecholaminergic systems (Yamamoto and Ueki, 1978). The LHA_A receives 5-HT input from the raphe (Veening et al., 1982; Vertes, 1991) and contributes efferent fibers that ascend or descend through the medial forebrain bundle (Saper et al., 1979; Hakan et al., 1992). We tested whether 5-HT released in the LHA_A may suppress sexual activity by inhibiting the mesoaccumbens DA system. In experiment 1 we used microdialysis to confirm previous electrochemical data showing increased NAcc DA release during copulation and decreased release after ejaculation. In experiment 2, we administered 5-HT to the LHA_A via reverse dialysis and simultaneously measured its effect on basal and female-elicited NAcc DA release.

MATERIALS AND METHODS

Subjects. Nineteen sexually experienced male rats were housed individually in plastic cages and maintained on a reverse light/dark cycle with lights off at 11:00 A.M. and on at 10:00 P.M. Food and water were available *ad libitum*. For experiment 1, 7 subjects received a unilateral

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Correspondence should be addressed to Dr. Elaine M. Hull, Department of Psychology, State University of New York at Buffalo, Buffalo, NY 14260.

Dr. Lorrain's present address: Department of Psychiatry, University of Chicago, MC 3077, 5841 South Maryland Avenue, Chicago, IL 60637.

Dr. Matuszewich's present address: Department of Psychiatry, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106-5000.

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guide cannula aimed at the shell region of the NAcc [anteroposterior, +3.0; mediolateral, +1.0; and dorsoventral, -5.2 (Pellegrino et al., 1979)]; the remaining 12 subjects, used in experiment 2, additionally received an ipsilateral guide cannula aimed at the LHA_A [anteroposterior, +1.3; mediolateral, +1.5; and dorsoventral, -7.2 (Pellegrino et al., 1979)]. After a 1 week period of recovery, microdialysis sessions began. All procedures followed the guidelines of and were approved by the local Institutional Animal Care and Use Committee.

Microdialysis. Concentric microdialysis probes were constructed in the lab. Briefly, a 27 ga thin-wall stainless steel tube was fitted with a dialysis membrane [12,000 kDa cutoff; 210 μ m outer diameter (o.d.); 1 mm active-dialyzing surface; Spectra Por, Houston, TX] at one end and a 3 cm piece of polyethylene 20 tubing at the other end to serve as the inlet for the perfusion medium. A 20 cm piece of silica capillary tubing [125 μ m o.d.; 50 μ m inner diameter (i.d.); Polymicro Technologies, Phoenix, AZ], threaded down into the dialysis tube, served as the outlet. For experiment 1, the dialysate flow rate was 1 μ l/min; samples were collected every 3 min into microcentrifuge tubes (250 μ l), placed on dry ice, and injected within 1 hr onto a capillary column for analysis of DA concentration by HPLC with electrochemical detection (HPLC-EC). For experiment 2, the dialysate flow rate was 0.5 μ l/min, and samples were collected every 10 min. For both experiments, the dialysis perfusion medium was a modified Ringer's solution consisting of 138 mM NaCl, 2.7 mM KCl, and 1.2 mM CaCl₂, pH 7.0. Flow was controlled by a Harvard syringe infusion pump (model 22; Cambridge, MA). On the morning of each microdialysis session, subjects were briefly anesthetized with ether to allow for insertion of the microdialysis probe(s). Flow of dialysate began immediately, and a 5 hr stabilization period was allowed before sample collection began. All microdialysis data are presented as percentage of baseline [which was established by taking the average of three consecutive prefemale (experiment 1) or predrug (experiment 2) samples].

HPLC. Detection of DA was accomplished using capillary HPLC-EC. Each sample was loaded manually into a VALCO self-actuating injector valve, delivering 500 nl to a C18 reverse-phase capillary column (0.3 mm i.d. \times 5.0 cm; 3 μ m spheres; LC Packings, San Francisco, CA). The mobile phase consisted of 30 mM citric acid, 50 mM sodium acetate, 0.027 mM Na₂EDTA, and 0.25 mM octyl sodium sulfate, with 2.5% acetonitrile and 0.2% tetrahydrofuran (v/v), pH 3.6, and was delivered using a Gilson, Inc. (Middleton, WI) model 307 pump operating at 0.5 ml/min and equipped with an Accurate flow splitter (LC Packings). The flow splitter provided 6 μ l/min of pulsation-free mobile phase to the analytical column. Dopamine oxidation was detected via an Antec DECADE controller (Leiden, The Netherlands) using a micro flow cell (11 nl volume) with a glassy carbon working electrode maintained at a potential of +0.7 V relative to a Ag/AgCl reference electrode. The system was calibrated daily with a freshly prepared DA standard at a concentration of 1 pg/ μ l (0.5 pg on the column).

Procedures. In experiment 1, after the 5 hr stabilization period and after collection of baseline dialysate samples, an estrous female was introduced into the male's testing arena, and copulation began. The male was allowed to copulate for up to three ejaculations. During this time, samples were collected in 3 min bins and labeled as those collected during copulation (COP) and those collected during sexual quiescence after an ejaculation (PEI). Three groups of samples (based on the male's behavior during collection) were thus established for subsequent HPLC analysis of DA content: baseline (BL), COP, and PEI.

In experiment 2, after the 5 hr stabilization period and after collection of baseline samples via the microdialysis probe located in the NAcc, flow was initiated in the probe located in the ipsilateral LHA_A, which delivered either 5-HT [1 mg/ml (5.6 mM); Sigma, St. Louis, MO] or vehicle (Ringer's solution). Dialysate samples continued to be collected from the NAcc in 10 min bins during 40 min of LHA_A perfusion. To test for 5-HT suppression of copulation-elicited NAcc DA release, we placed an estrous female into the male's testing arena during collection of the final sample, concurrent with LHA_A 5-HT perfusion (i.e., time, 30–40 min after baseline). All males displayed some sexual behaviors; however, their performance was not scored.

Histology. After the microdialysis session, animals were deeply anesthetized with sodium pentobarbital, and cresyl violet dye was perfused through their microdialysis probe(s). Subjects were then decapitated, and their brains were removed for histological verification of probe placement. Only those animals with blue dye in the region of the NAcc (experiment 1) and LHA_A (experiment 2) were used for statistical analysis.

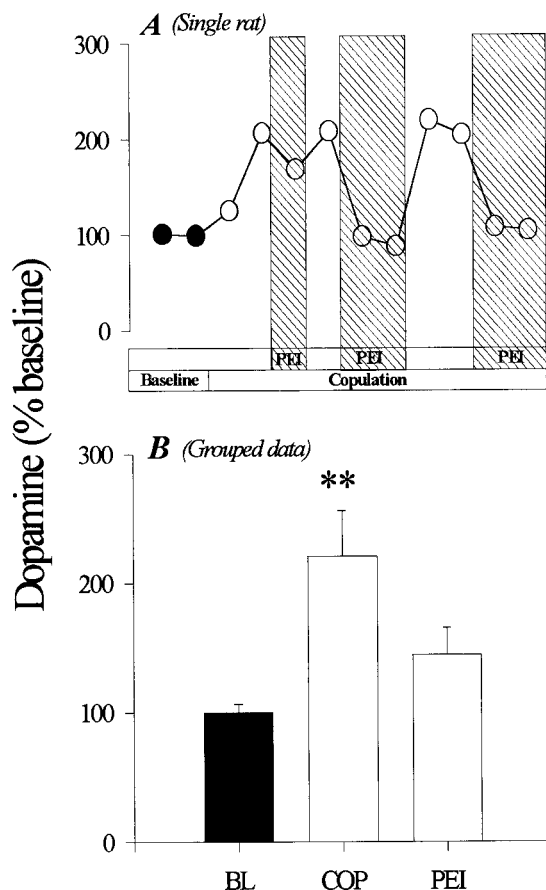


Figure 1. *In vivo* microdialysis of DA release from the NAcc of male rats during sexual behavior sessions. *A*, Representative example of temporal changes in a single rat. *B*, Mean change in DA release (\pm SEM) for a group of six rats. Samples were collected at 3 min intervals during three ejaculatory series and are designated precopulatory BL (filled circles), COP (open circles), or PEI (hatched circles). Dopamine content was significantly greater in samples collected during copulation, compared with samples collected under BL and PEI conditions (** $p < 0.05$).

Data analysis. For experiment 1, as noted above, dialysate collected from the NAcc was grouped into three behavioral categories: BL, COP, and PEI (expressed as percentages). A one-way ANOVA was conducted on the mean DA percentages for these three groups. Because the test for normality failed ($p < 0.001$), a Kruskal–Wallis one-way ANOVA on ranks was performed, followed by *post hoc* comparisons using the Dunn's method. For experiment 2, a two-way repeated measures ANOVA was used, with perfusate (5-HT vs vehicle) as the between factor and time (6 or 10 min dialysis bins) as the within factor, to test the effects of 5-HT perfusion into the LHA_A on NAcc DA levels. *Post hoc* Scheffé comparisons were made according to Kirk (1968).

RESULTS

Experiment 1: DA release in the NAcc during copulation and after ejaculation

DA release in the NAcc followed a predictable pattern reflective of an activational role for this neurotransmitter in copulation. A typical pattern for an individual animal can be seen in Figure 1*A*; DA release was high during copulation but decreased after each ejaculation (i.e., during the PEI). The ANOVA on ranks for the grouped data revealed a significant difference in mean dialysate DA levels across behavioral categories [$H(2) = 14.794$; $p < 0.001$; Figure 1*B*]. *Post hoc* comparisons showed that DA was significantly higher in samples collected during copulation, compared with those collected during either BL or the PEI ($p < 0.05$).

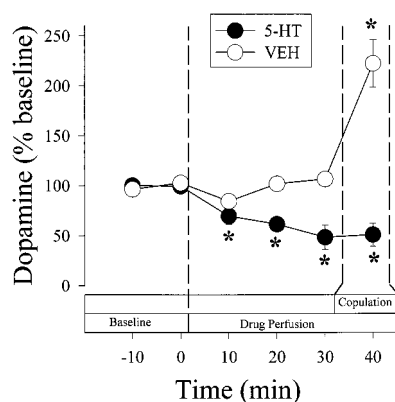


Figure 2. Temporal change in DA concentration of the dialysate collected from the NAcc before and during 40 min of 5-HT perfusion into the LHA_A of six male rats. Samples were collected at 10 min intervals. An estrous female was introduced to the male, and copulation was allowed during collection of the final sample during 5-HT perfusion. A significant decrease in DA occurred throughout the entire 5-HT perfusion period. This treatment blocked the increase in NAcc DA release seen in control animals [$*p < 0.05$, perfusion times vs time 0 (baseline)]. VEH, Vehicle.

Experiment 2: effects of 5-HT in the LHA_A on DA in the NAcc

Reverse dialysis of 5-HT into the LHA_A decreased the basal release of NAcc DA and also prevented the enhanced release normally seen during copulation (Fig. 2). The ANOVA conducted on these data detected a significant effect of groups [$F_{(1,10)} = 46.324$; $p < 0.001$] and time [$F_{(5,50)} = 11.232$; $p < 0.001$] and a group \times time interaction [$F_{(5,50)} = 22.876$; $p < 0.001$]. *Post hoc* comparisons revealed that DA was significantly lower in each of the four dialysate samples collected during 5-HT perfusion, compared with baseline values ($p < 0.05$). Animals receiving vehicle into the LHA_A showed a significant increase in NAcc DA relative to baseline ($p < 0.05$) during copulation; however, no such increase was observed in the animals receiving 5-HT into the LHA_A.

DISCUSSION

These findings demonstrate a neurochemical link between the hypothalamic and mesolimbic systems of the brain that may promote sexual quiescence during the PEI. In experiment 1 we established that extracellular DA levels increase in the NAcc of male rats during copulation but then decrease after ejaculation, during the PEI. Similar results have been reported, based on *in vivo* chronoamperometric techniques (Phillips et al., 1991). Although such techniques have high temporal resolution, they cannot completely dissociate the contributions of DOPAC and ascorbic acid from that of DA to the signal (Dayton et al., 1981; Gonon et al., 1984). Recently, using *in vivo* microdialysis, which has excellent neurochemical resolution, Fiorino et al. (1997) concluded that sexual satiation may be related to an inability of an estrous female to elicit an increase in NAcc DA levels. In that experiment a 15 min sampling period was used, preventing a description of individual ejaculatory sequences. The present experiment used a 3 min sampling interval, providing for the first time both high temporal resolution and neurochemical resolution in a fine-grained analysis of DA release during specific behavioral episodes. The enhancement of NAcc DA release during copulation was not maintained throughout the PEI. This suggests that

the DA-enhancing properties of the estrous female are somehow filtered or inhibited immediately after an ejaculation.

Lateral hypothalamic 5-HT levels, which increase after ejaculation, may contribute to the sexual quiescence of the PEI. Administering 5-HT into the LHA_A via reverse dialysis in experiment 2, like ejaculation, produced an immediate decrease in the extracellular levels of DA in the NAcc. Dopamine continued to decline steadily throughout 5-HT administration. This treatment also prevented the female-elicited DA increase that is normally associated with copulation.

We reported recently that extracellular 5-HT increased in the LHA_A after ejaculation; microinjection of an SSRI into this region delayed the onset of sexual activity (similarly to the PEI) and also delayed ejaculation after copulation began but did not interfere with general locomotion (Lorrain et al., 1997). These data, together with the current findings, suggest that the abrupt halt in copulation after an ejaculation may be, in part, regulated by the release of 5-HT in the LHA_A and the consequent inhibition of mesoaccumbens DA. Under normal conditions, DA is released within the NAcc of male rats when estrous cues are present (Loulot et al., 1991; Damsma et al., 1992). This DA may activate the male to copulate with the female. DA-depleting lesions of the NAcc decreased the number of penile erections in response to remote stimuli from an estrous female and delayed the onset of copulation (Liu et al., 1998). During the PEI, NAcc DA levels decrease (experiment 1), as does the display of sexual advances toward a female. The rise of 5-HT in the LHA_A may be an important factor inhibiting neuronal processes that normally activate mesoaccumbens DA and appetitive behaviors.

Inhibitory control over copulation during the PEI is an important factor in reproductive success. Too early resumption of copulation would dislodge the sperm plug that promotes sperm transport to the female's uterus (Adler and Zoloth, 1970; Sachs, 1982); furthermore, a second ejaculate occurring soon after the first would have fewer sperm than the preceding one. The sexual quiescence of the PEI is not a result of erectile failure; reflexive erections are maintained, or actually enhanced, by a preceding ejaculation (O'Hanlon and Sachs, 1980). Therefore, it is important for the male (and female) to be motivationally inhibited during the PEI to promote a successful pregnancy. The concurrent decrease in LHA_A 5-HT (Lorrain et al., 1997) and increase in NAcc DA at the end of the PEI suggest a means for timing this period of sexual quiescence. The observation of two concurrent processes does not establish the direction of causation. However, the finding that reverse dialysis of 5-HT into the LHA_A decreases extracellular levels of DA in the NAcc suggests that the postejaculatory rise in 5-HT in the LHA_A normally causes the decrease in NAcc DA.

The LHA_A may be well suited for modulating sexually relevant information from the hypothalamus to the rest of the brain. The lateral zone of the hypothalamus has been described as controlling arousal and motivated behavior (Benarroch, 1993). Numerous neurons in the lateral hypothalamus (LH) rapidly changed their firing rates in response to jugular injections of either testosterone or estrogen (Orsini, 1982) and also to direct application of these hormones (Orsini, 1985). Furthermore, semiquantitative 2-deoxyglucose analysis of neural activation revealed an increase of neural activity in the LH in response to female odors (Orsini et al., 1985). Therefore, LH neurons may promote male sexual interest and/or activity. In addition, parasagittal cuts separating the MPOA from the LHA_A/medial forebrain bundle impaired

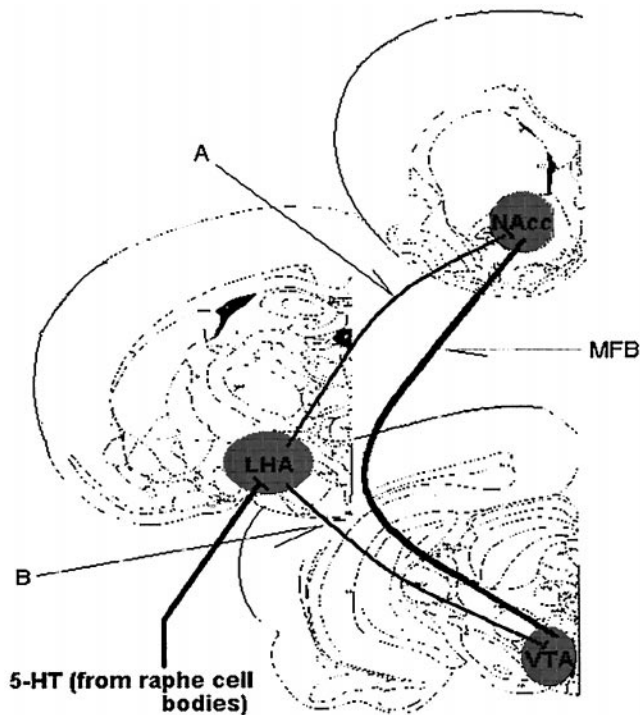


Figure 3. Schematic representation of possible neural circuits involved in LHA_A 5-HT inhibition of NAcc DA release. DA release may be influenced from 5-HT acting on direct projections from the LHA_A to the NAcc (A) or indirect projection neurons reaching the VTA (B). Adapted from Paxinos and Watson (1982). MFB, Medial forebrain bundle.

copulation in male rats (Szechtman et al., 1978; Brackett and Edwards, 1984).

There are at least two potential pathways that may mediate LHA_A 5-HT influences on NAcc DA release (Fig. 3). The LHA is included in a group of structures that comprise the subpallidal area, which has been shown to have reciprocal connections with the NAcc (Hakan et al., 1992; Wu et al., 1996). There is also anatomical evidence of a descending pathway from the LH to the ventral tegmental area (VTA) (Wolf and Sutin, 1966; Saper et al., 1979). Thus, DA release in the NAcc could be directly influenced via the ascending pathway from the LHA to the NAcc or indirectly modulated via the descending pathway from the LHA to the VTA.

The NAcc terminal field is comprised of two main subregions, the shell and the core (for review, see Deutch et al., 1993). In the present study, microdialysis probe placements were restricted to the shell and therefore reflect LHA_A 5-HT control over this subregion. It is unclear whether the core is similarly influenced. Such information may provide insight into differences between these two subregions in the control of motivated behaviors.

Although copulation did not elicit a DA response in the NAcc ipsilateral to the 5-HT reverse dialysis (experiment 2), all males were able to copulate, possibly because of normal DA activity in the unaffected contralateral hemisphere. Behavioral parameters were not recorded, so it is impossible to know whether 5-HT animals were different from controls. However, bilateral microinjections of an SSRI into the LHA_A did delay and slow copulation in a previous experiment (Lorrain et al., 1997). DA-depleting lesions of the NAcc also delayed copulation onset (Liu et al., 1998), and decreasing NAcc DA release delayed and slowed

copulation (Hull et al., 1991), suggesting that the NAcc DA is not necessary for copulation but does promote its onset.

These findings may have relevance for serotonergic control over other behaviors. Mesoaccumbens DA activity contributes to the activational impetus for many forms of motivated behavior (Koob, 1996; Salamone et al., 1997). The fact that increased extracellular 5-HT in the LHA_A can inhibit NAcc DA release suggests that increased LHA_A 5-HT may affect many behaviors. For example, extracellular DA in the NAcc is elevated before and during consumption of a meal and falls sometime afterward (Wilson et al., 1995). Furthermore, LHA 5-HT release increases during meal consumption and has been suggested as one factor promoting satiety (Schwartz et al., 1989; Aoyagi et al., 1992). DA, as well as 5-HT, in the LHA may inhibit NAcc DA release and behavioral reinforcement (Parada et al., 1995). Therefore, both 5-HT and DA release in the LHA_A may form part of the neural circuitry responsible for terminating appetitive behaviors, perhaps by inhibiting stimulus-bound NAcc DA activation.

The present data may also provide insight into the effects of altered 5-HT activity on electrical self-stimulation of the brain and intravenous drug self-administration. These behaviors are under the control of mesoaccumbens DA activity (for review, see Di Chiara, 1995) and can be enhanced or inhibited by decreasing or increasing, respectively, 5-HT neurotransmission [electrical brain stimulation (Poschel and Ninteman, 1971; Katz and Carroll, 1977; Montgomery et al., 1991; Olds and Yuwiler, 1992; Fletcher et al., 1995) and intravenous drug self-administration (Carroll et al., 1990a,b; Loh and Roberts, 1990; Richardson and Roberts, 1991)]. There is, however, a recent report showing that stimulation of the 5-HT_{1B} receptor subtype may actually enhance cocaine reinforcement and thus cocaine self-administration behavior (Parsons et al., 1998). Nonetheless, the present findings suggest a central site that may mediate the suppressive effects of 5-HT on self-stimulation and -administration behaviors. Thus, LHA_A 5-HT may be an important factor to consider when developing strategies for the treatment of drug abuse.

In conclusion, extracellular DA in the NAcc increased during copulation but then decreased after ejaculation. Elevating LHA_A 5-HT via reverse dialysis decreased extracellular DA during both basal conditions and copulation. These data, together with previous findings (Lorrain et al., 1997), suggest that LHA_A 5-HT exerts inhibitory control over copulation, in part, by inhibiting NAcc DA release after an ejaculation. This research has important clinical implications for those taking SSRI antidepressants, major side effects of which are impairment of ejaculatory and orgasmic ability and decreased libido. It also suggests a central site in which 5-HT may exert inhibitory control over other motivated behaviors.

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