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A D_1 Agonist in the MPOA Facilitates Copulation in Male Rats

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MARKOWSKI, V. P., R. C. EATON, L. A. LUMLEY, J. MOSES AND E. M. HULL. *A D_1 agonist in the MPOA facilitates copulation in male rats.* PHARMACOL BIOCHEM BEHAV 47(3) 483-486, 1994.—The classic dopamine agonist apomorphine, microinjected into the medial preoptic area (MPOA), enhances the copulatory behavior of male rats, while pharmacological blockade of endogenous dopamine inhibits sexual behavior. We now report that MPOA injections of 10 μg of the selective D_1 agonist dihydroxyphenyl-tetrahydrothienopyridine (THP) significantly increased the number of ejaculations, while decreasing the latency to ejaculate in a 30-min test. These effects were not observed following coadministration of the selective D_1 antagonist SCH-23390 with 10 μg THP. This enhancement may be related to a D_1-stimulated facilitation of penile erections.

Dihydroxyphenyl-tetrahydrothienopyridine (THP) Dopamine D_1 receptor Copulation Medial preoptic area

DOPAMINERGIC drugs facilitate sexual behavior in men and male rats (3). Copulatory behavior of the male rat is a complex process requiring the integration of genital, motivational, and somatomotor systems. One brain site where dopaminergic activity appears to facilitate all three of the above behavioral factors is the medial preoptic area (MPOA) (15, 20,23).

Dopamine in the MPOA influences genital reflexes, probably through disinhibition of spinal motoneurons that control the striated penile muscles, and through autonomic influences. Relatively low doses of the nonselective dopamine agonist apomorphine increased the numbers of erections and penile anteroflexions in restrained supine rats (9,15). Opposite effects were noted after MPOA administration of the dopamine antagonist *cis*-flupenthixol (23). Dopamine in the MPOA also contributes to sexual motivation. *cis*-Flupenthixol administered into the MPOA decreased the number of trials in which a male chose to be with a receptive female, as measured in an X-maze (23). This effect did not result from general locomotor impairment, since neither the speed to reach a goalbox nor the number of failures to move from the central area of the maze was affected. Thus, the previously observed facilitation of copulation after administration of apomorphine into the MPOA (8) may result from a combination of enhanced genital reflexive ability and sexual motivation.

Two families of dopamine receptors have been widely recognized. D_1 receptors stimulate adenylate cyclase, and D_2 receptors either inhibit or do not affect this enzyme (12). The use of selective D_1 and D_2 receptor agonists and antagonists affords the opportunity to investigate the contributions of the two subtypes to the copulatory behavior of the male rat. Selective stimulation of D_2 or inhibition of D_1 receptors in the MPOA delayed the onset of copulation, slowed its rate, and decreased the number of vaginal intromissions preceding ejaculation (11). We now report that a D_1 agonist injected into the MPOA increased the number of ejaculations by decreasing the latency to ejaculate.

METHOD

Subjects

Adult male Long-Evans rats (Harlan Sprague-Dawley/Blue Spruce, Altamont, NY) were housed individually in large plastic cages with food and water available ad lib. Animals were handled daily so that microinjections could be administered without anesthesia. They were tested for copulation three times before surgery; only those that copulated consistently were chosen.

Ovariectomized females of the same strain were used as stimulus animals and were housed in a separate room. Females

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were brought into behavioral estrus with a single SC injection of estradiol benzoate (20 μg in oil) 48 h before behavioral testing. All animals were housed in temperature- and humidity-controlled rooms. Lights were off from 1100 to 2100.

Surgery and Cannulae

The male rats were anesthetized with ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (4 mg/kg) IM and received a unilateral stainless steel guide cannula ending 1 mm above the left MPOA [from bregma: anterior-posterior (AP) = +2.4, medial-lateral (ML) = +0.2, dorsal-ventral (DV) = −7.0, incisor bar = +5 (16)]. The guide cannulae were constructed of 23-gauge thin-wall stainless steel tubing (o.d. = 0.6 mm, i.d. = 0.4 mm). An obturator constructed from 27-gauge stainless steel tubing (o.d. = 0.4 mm, i.d. = 0.2 mm) was cut flush with the end of the guide cannula and remained in the guide cannula except during microinjections. Injection cannulae were also constructed from 27-gauge tubing and extended 1 mm below the end of the guide cannula. Details of surgery and cannula construction are described in (8).

Drugs

The selective D_1 agonist THP was generously donated by Dr. David E. Nichols (Purdue University). Doses of 0.0, 1.0, and 10.0 μg were dissolved in 0.5 μl of 0.2% ascorbate and injected into the MPOA of 21 animals with accurate cannula placements. At the conclusion of the experiment, a subgroup of these animals (n = 13) received the D_1 selective antagonist SCH-23390 (a generous gift of Dr. A. Barnett, Schering Plough) together with THP: 10 μg SCH + 10 μg THP in 1 μl 10% Me_2SO.

Procedures

Two weeks following surgery, animals were given a single postoperative baseline test for sexual behavior. Thereafter, behavioral tests were given at one-week intervals. All animals received all doses in a counterbalanced order. Drugs were administered using a Harvard infusion pump while the animal moved freely in his cage. The rate of injection was 1.0 μl/min, with the injection cannula being left in place for 30 s after the injection was completed. The male was then carried in his home cage to an adjacent testing room, where a stimulus female was introduced into his cage. Testing began immediately.

Each test lasted for 30 min following the first intromission, or for a total of 30 min if the male failed to intromit. The occurrence and time of each mount, intromission, and ejaculation were recorded. Measures derived from the data were number of ejaculations per test, number of mounts and intromissions preceding each ejaculation, latencies to the first mount and the first intromission, ejaculation latency (time from the first intromission of an ejaculatory series to the subsequent ejaculation), postejaculatory refractory time (time from the ejaculation to the next intromission), interintromission interval (the average time between intromissions), and intromission ratio (the number of intromissions divided by the number of mounts plus intromissions). Intromissions were distinguished behaviorally from mounts without intromission by the presence of a single deep pelvic thrust followed by a rapid, springing dismount. Ejaculation patterns were characterized by longer, deeper thrusts, slow dismounts, and a prolonged period of rest following ejaculation.

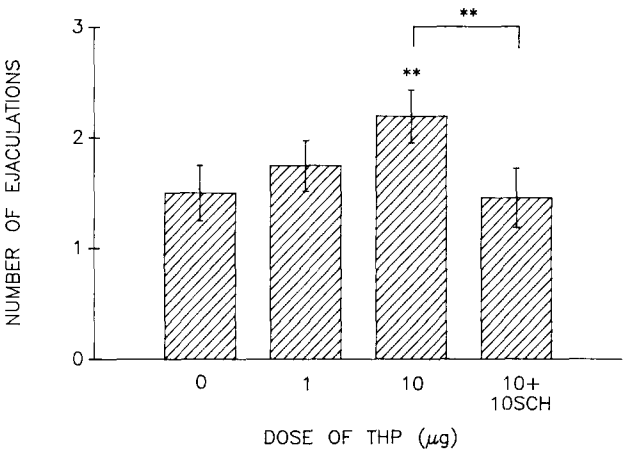

FIG. 1. Effects of MPOA injections of the D_1 agonist dihydroxyphenyl-tetrahydrothienopyridine (THP) and of THP plus the D_1 antagonist SCH-23390 on ejaculation frequency. Values are means ± SE. $^{**}p < .01$.

Cannula placements were verified histologically. Twenty-one animals that copulated on at least two of the four experimental test sessions and that had histologically verified MPOA cannulae were included in the data analysis. Data were analyzed by repeated-measures analyses of variance (ANOVAs) followed by Newman-Keuls post hoc tests. Log transformation of the ejaculation latency was utilized to achieve homogeneity of variance.

RESULTS

The D_1 agonist THP significantly increased the number of ejaculations per 30-min test, $F(2, 38) = 4.87$, $p < .01$ (Fig. 1). A reduced ejaculation latency, $F(2, 38) = 3.83$, $p < .05$ (Fig. 2), was a major factor in the increased number of ejaculations observed per 30-min test. No other measure was significantly affected, although a decrease in the interintromission interval approached statistical significance ($.05 < p < .1$).

In addition, the D_1 selective antagonist SCH-23390 blocked

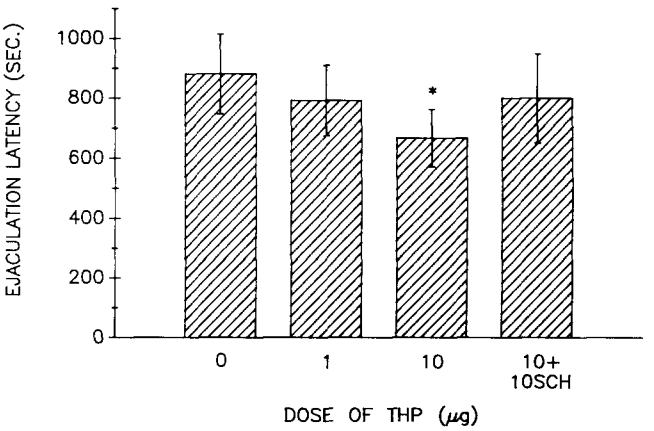

FIG. 2. Effect of MPOA injections of the D_1 agonist dihydroxyphenyl-tetrahydrothienopyridine (THP) and of THP plus the D_1 antagonist SCH-23390 on the latency to ejaculate. Values are means ± SE. $^{*}p < .05$.

the increase in number of ejaculations when administered to a subgroup of 13 animals—t = 0.12, NS, Veh. vs. 10 THP + 10 SCH; t = 3.27, $p < .01$, 10 THP vs. 10 THP + 10 SCH—by returning the ejaculation latency to baseline levels, t = 0.84, NS, Veh. vs. 10 THP + 10 SCH).

DISCUSSION

Administration of a D_1 agonist into the MPOA of male rats significantly increased the number of ejaculations during a 30-min copulatory session. One factor in the present D_1-mediated speeding of copulatory rate may be a selective enhancement of genital reflexes. A D_1 agonist administered to the MPOA increased the number of ex copula erections. This facilitation of erectile mechanisms was at the expense of ejaculatory mechanisms, which were inhibited by the D_1 agonist (9). Conversely, a D_2 agonist administered to the MPOA decreased erections, while increasing seminal emissions (1). This inverse relationship suggests that the D_1/D_2 ratio is an important factor in the regulation of male sexual behavior. Furthermore, the D_1 facilitation of erections appears to have a lower threshold than the D_2 facilitation of seminal emissions (9).

Other behaviors affected oppositely by D_1 and D_2 stimulation include D_1-mediated repetitive jaw movements and tongue thrusting (19) and grooming (22). Both behaviors are inhibited by D_2 stimulation. These results contrast with the D_1/D_2 receptor synergism observed in most behaviors [reviewed in (6)]. For example, rats depleted of endogenous dopamine by alpha-methyl-para-tyrosine pretreatment require concurrent D_1 and D_2 agonist stimulation to reestablish unconditioned behaviors such as locomotor/exploratory activity and stereotypy (5). Both synergistic (2,17) and antagonistic biochemical effects have been reported (14,21).

The direction of D_1/D_2 interaction varies across brain structures. Synergistic effects have been observed in globus pallidus, substantia nigra pars compacta, subthalamic nucleus, central amygdala, and the dorsal and ventral horn (18), whereas D_2 agonists inhibited D_1 excitation of neurons in substantia nigra pars reticulata (7), superior colliculus, and olfactory and temporal cortices (18).

We suggest that the differential behavioral effects of D_1/D_2 receptor stimulation in the MPOA may reflect similar functions of fluctuating levels of endogenous dopamine. Blackburn et al. (4) reported that catecholamine release in the MPOA, measured with chronamperometry, increased as soon as a male rat confronted a receptive female, and remained high throughout the copulatory sequence. The amperometric signal peaked immediately prior to ejaculation, after which it fell sharply. A gradual increase in catecholamine release preceded the initiation of a new copulatory series. Although these researchers were unable to resolve the relative contributions of dopamine and norepinephrine to their signal, others have reported an increase in dopamine and its metabolites, but not norepinephrine, following ejaculation, using high-performance liquid chromatography with electrochemical detection (HPLC-EC) analyses of MPOA tissue punches (13) and microdialysis (10). An early increase of dopamine activity may mediate enhanced erectile mechanisms and sexual motivation, which would serve to bring the male rat into contact with a receptive female and initiate and maintain copulation. Peak dopamine concentrations just prior to ejaculation may switch from copulatory to ejaculatory mechanisms, mediated by D_2 receptors, as discussed in (9).

In conclusion, the initiation of a sustained release of endogenous dopamine in the male rat MPOA is correlated with the onset and maintenance of copulation. Furthermore, MPOA infusions of a D_1 agonist, or low doses of the D_1/D_2 agonist apomorphine, enhance both genital reflexes and the rate of copulation. Thus, successive activation of D_1- and D_2-mediated mechanisms may maintain copulatory activity and then facilitate ejaculation.

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