Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 4, pp. 883–888, 1994

0091-3057/94 $6.00 + .00

Serotonergic Neurotoxic Lesions Facilitate Male Sexual Reflexes

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Received 15 March 1993

MARSON, L. AND K. E. McKENNA. *Serotonergic neurotoxic lesions facilitate male sexual reflexes.* PHARMACOL BIOCHEM BEHAV 47(4) 883–888, 1994.—The effects of the neurotoxin 5,7 dihydroxytryptamine (5,7 DHT) on the urethrogenital reflex was examined in anesthetized male rats. Both ICV and intrathecal administration of 5,7 DHT produced a marked depletion (92%) of spinal 5-hydroxytryptamine (5-HT) and 5-hydroxyindole acetic acid (5-HT IAA) levels. ICV but not intrathecal administration of 5,7 DHT also caused a moderate reduction in 5-HT and 5-HT IAA levels in the medulla and hypothalamus (40–48%). No reduction in adrenergic levels were observed. In spinally intact, vehicle-treated rats the urethrogenital reflex could not be evoked. However, the urethrogenital reflex could be evoked in rats pretreated with either ICV or intrathecal 5,7 DHT prior to section of the spinal cord. These data support the hypothesis that 5-HT mediates the descending inhibition of male sexual reflexes.

5-Hydroxytryptamine Sexual reflexes Ejaculation Descending pathway Urethrogenital reflexes

THE urethrogenital (UG) reflex is a sexual reflex evoked by urethral stimulation in the anesthetized rat. The UG reflex consists of coordinated rhythmic firing of autonomic and somatic efferents. We have provided evidence that the UG reflex represents the neural concomitants of sexual climax in the male and female rat (8,29). The UG reflex involves a multisegmental coordination of sympathetic, parasympathetic, and somatic activity and is inhibited by tonically active neurons in the region of the rostral nucleus paragigantocellularis (nPGi) (23). Neurons in the nPGi not only control the inhibition of the UG reflex but also inhibit sexual reflexes in ex copula tests (25). In addition, chronic lesions of the nPGi result in an increased copulatory efficiency (35).

5-Hydroxytryptamine (5-HT) has been shown to exert both an inhibitory and excitatory influence over sexual reflexes and sexual behavior (1,10). We previously reported the presence of 5-HT containing neurons in the nPGi that project to the lumbosacral cord (23,24). In addition, intrathecal administration of 5-HT inhibited the UG reflex in spinalized animals (24). If release of 5-HT tonically inhibits the UG reflex, then destruction of 5-HT containing fibers should allow the UG reflex to be exposed prior to spinal cord transection. 5,7 Dihydroxytryptamine (5,7 DHT) is a neurotoxic compound that is selectively taken up by tryptaminergic neurons and thereby causes selective degeneration of these neurons (3). The present study examines the effects of intracerebroventricular ICV or intrathecal injection of 5,7 DHT on the presence of the UG reflex before and after spinal cord transection.

METHOD

Intrathecal Cannulation

Male Sprague-Dawley rats (n = 43, Charles River, 260–330 g) were anesthetized with ketamine/xylazine [ketamine 90 mg/kg (Aveco) xylazine 15 mg/kg (Rugby)] for placement of an intrathecal catheter. The intrathecal catheter (PE 10 tubing, extending 7.5–8 cm into the subarachnoid space) was prefilled with sterile saline. Rats were placed in a stereotaxic instrument with the head tilted downward. The catheter was inserted through a hole in the atlanto-occipital membrane, into the subarachnoid space until it reached the lumbar cord. The catheter was secured to the skull with the aid of acrylic cement, the skin was sutured and the free end of the catheter was allowed to protrude from the skull through the skin. Rats were housed singly and allowed to recover from surgery for one week.

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5,7 Dihydroxytryptamine (5,7 DHT) Injections

All rats were pretreated with desimipramine (25 mg/kg IP) 20–40 min prior to 5,7 dihydroxytryptamine creatinine sulphate (5,7 DHT) or vehicle injections to prevent uptake of 5,7 DHT by adrenergic uptake systems. The 5,7 DHT was calculated as free base and made up in 0.1 M ascorbic acid. Groups of rats were anesthetized with isofluorane (2–4% in O_2) and 5,7 DHT or vehicle was administered either ICV (n = 14) or intrathecally (n = 29) under sterile conditions. For ICV injections rat were placed into a stereotaxic apparatus and a small hole was drilled in the skull. A Hamilton syringe was lowered into the third ventricle (coordinates 0.8 mm caudal to bregma, 1.5 mm lateral, and 4.2 mm deep) and 5,7 DHT (200 μg in 10 μl) or vehicle was injected over 1 min. The syringe was removed, the hole sealed with bone wax, and the skin overlying the skull sutured. Intrathecal injections (50 μg in 10 μl) were followed with a 10 μl sterile saline flush to ensure complete delivery of the drug. The tip of the PE 10 catheter was heat sealed after the injection. To avoid any irritant effects of the drug administration rats were maintained on isofluorane 5–10 min after injections. The rats receiving ICV injections were injected with sodium pentobarbital (65 mg/ml IP) prior to removal of the isofluorane.

Recording the Urethrogenital Reflex

Rats were anesthetized with urethane (1.2–1.5 g/kg IP or SC) 10–12 days after 5,7 DHT or vehicle injections. The carotid artery and jugular vein were cannulated for measurement of arterial blood pressure and infusion of drugs or fluids, respectively. The trachea was cannulated for artificial respiration using a Harvard rodent respirator. A catheter was inserted into the urethra via a bladder incision and was tied in place. The urethral catheter was connected to an infusion pump and pressure transducer. The sensory and motor branches of the pudendal nerve were carefully exposed via a dorsal approach. Neural recordings were made with bipolar silver wire hook electrodes spaced approximately 1 mm apart. The surgical area was filled with warm mineral oil to prevent dehydration. Rats were maintained at 38°C with a thermostatically controlled heating blanket. Recording signals were fed into an high impedance preamplifier, displayed onto a polygraph and oscilloscope and fed to an audio monitor and digital tape recorder. The urethrogenital (UG) reflex was elicited by urethral distension accomplished by infusing saline through the urethral catheter and briefly occluding the urethral meatus (21,27). Presence of the UG reflex was examined in the spinally intact rat. Immediately after testing for the reflex in the spinally intact rat, transections of the spinal cord were made at C1 and the presence of the UG reflex further examined. The threshold pressure required to elicit the UG reflex as well as the onset latency, duration, and number of bursts were monitored.

Measurement of Monoamines

Immediately following recordings of the UG reflex, rats were decapitated and the lumbosacral cord, medulla, and hypothalamus removed. Tissue was homogenized in 0.1 N perchloric acid (500 μl) containing 0.1 M sodium metabisulphite, centrifuged at 1500 rpm for 15 min, and the supernatant removed and stored at −70°C until assayed using high pressure liquid chromatography (HPLC). A 50 μl sample was taken prior to centrifugation for protein assay (21). All samples were measured 2–3 days after extraction. Quantification was performed by comparison of peak heights against 5-HT, 5-hydroxyindoleacetic acid (5-HT IAA) and norepinephrine (NE) standards.

Data Analysis

Data were analyzed using the Student's t-test or analysis of variance followed by the Scheffe F-test, depending on the number of groups.

RESULTS

In the intact rat the UG reflex cannot be evoked. However, genital stimulation can evoke the UG reflex after spinal cord transection (SCT) or lesions of the ventral medulla (8,23,29). In the present study genital stimulation did not evoke the UG reflex in the nonspinalized vehicle-treated group. However, pretreatment with 5,7 DHT did allowed the UG reflex to be uncovered prior to spinal cord transection.

HPLC Data

ICV administration of 5,7 DHT reduced levels of 5-HT by 92% in the lumbosacral spinal cord, 48% in the medulla, and 40% in the hypothalamus. Intrathecal (IT) administration of 5,7 DHT reduced spinal 5-HT levels by 92% but did not significantly reduce 5-HT levels in the medulla or hypothalamus. Figure 1 shows the effect of ICV and intrathecal administration of 5,7 DHT on 5-HT and 5-HT IAA concentrations in the lumbosacral spinal cord, medulla, and hypothalamus. There were no significant changes in noradrenaline concentrations in either the lumbosacral spinal cord, medulla, or hypothalamus (Table 1).

The Effects of 5,7 DHT on Urethrogenital (UG) Reflexes

Prior to section of the spinal cord the UG reflex was not present in the control group. However, the UG reflex was present prior to spinal cord transection in 86% of the ICV and 50% of the intrathecal 5,7 DHT-pretreated rats. Figure 2 shows examples of the UG reflex in a 5,7 DHT and vehicle-treated rat, before and after transection of the spinal cord. The pressure threshold required to elicit the UG reflex in the 5,7 DHT-treated animals was significantly higher than that required after spinal cord transection in both 5,7 DHT and vehicle-treated rats (for ICV $F(16) = 15.627$, $p < 0.002$; for IT group $F(20) = 16.784$, $p < 0.001$; Fig. 2 and Table 2). In addition, the onset latency of the UG reflex prior to spinal cord transection in the 5,7 DHT group was significantly longer than that seen after spinal cord transection in either the 5,7 DHT or vehicle group [for ICV, $F(16) = 6.171$, $p < 0.0103$; for IT, $F(22) = 8.283$, $p < 0.002$]. There were no differences in the duration of the UG reflex after IT injections, $F(22) = 0.297$ $p < 0.7455$. However, after ICV 5,7 DHT, the duration of the UG reflex was significantly longer than any other group, $F(16) = 6.769$, $p < 0.0073$. The number of bursts was similar in all groups (Table 2). After spinal cord transection the UG reflex in the 5,7 DHT-treated group was the same as in the vehicle-treated group (Table 2).

DISCUSSION

The present study demonstrates that selective destruction of 5-HT descending pathways allows the elicitation of the UG reflex in the nonspinalized anesthetized rat. The UG reflex is not normally present in this preparation prior to spinal cord transection or bilateral lesions of the nPGi (8,23). We pre-

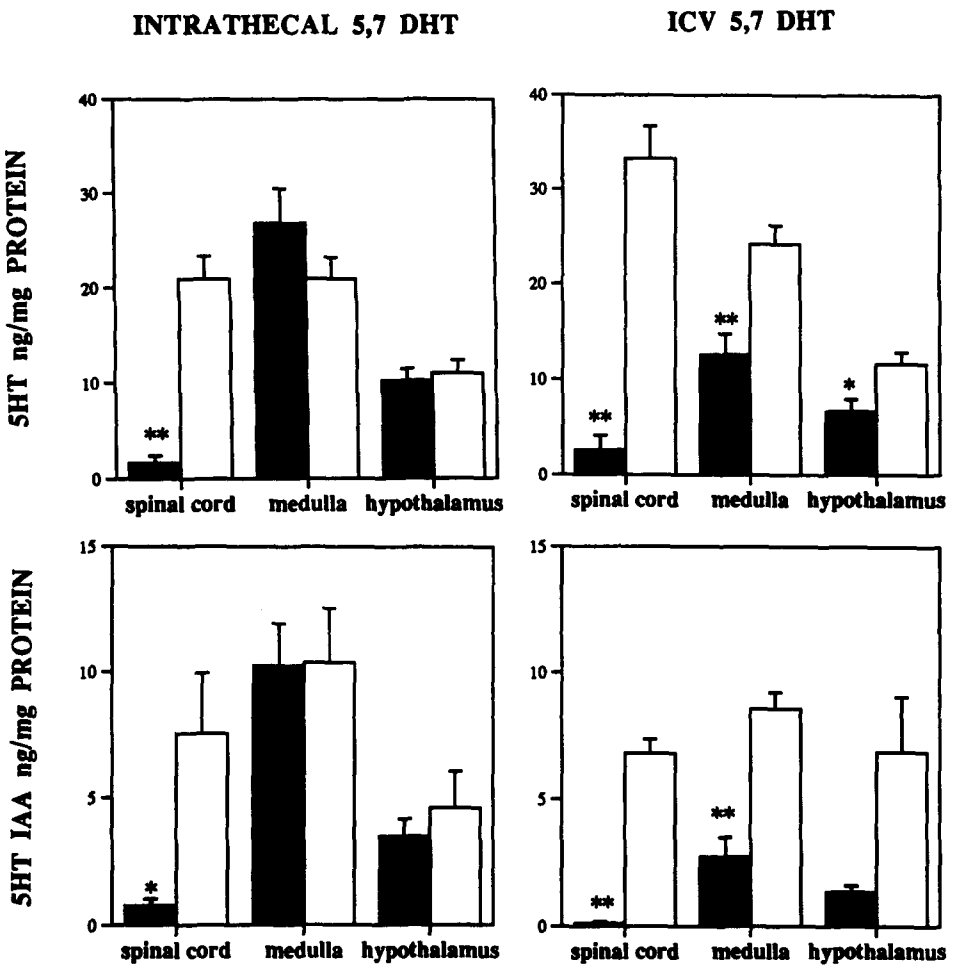

FIG. 1. Histograms illustrating 5-HT and 5-HT IAA concentrations in the lumbosacral spinal cord, medulla, and hypothalamus in control (open bars) and 5,7 DHT-treated (filled bars) rats after either intrathecal or ICV injections. Values are mean ± SE for 6–10 rats/group. *Denotes a significant difference between control and 5,7 DHT-treated rats $*p < 0.05$, $**p < 0.001$ (t-test).

viously presented anatomical and pharmacological evidence for the control of the descending inhibition of spinal sexual reflexes by 5-HT-containing neurons in the nPGi (23,24). The present study extends and confirms our previous findings.

5-HT-containing neurons in the nPGi project directly to the lumbosacral cord in the vicinity of the pudendal motoneurons and autonomic areas known to innervate the genitalia (5,15,23,24). In addition, 5-HT immunoreactive fibers and presumptive terminals are present in the lumbosacral cord around sympathetic and parasympathetic preganglionic neurons and pudendal motoneurons (15,24,34). Moreover, transneuronal tracing studies have shown 5-HT immunoreactive virus labeled neurons in the nPGi after injections of the pseudorabies virus (PRV) into the penis (26). These studies provide anatomical evidence for a regulation of sexual reflexes by serotonergic neurons in the nPGi. The inhibitory effect of serotonin may be mediated by pudendal motoneurons and preganglionic neurons directly or via interneurons in the region of the intermediolateral cell column and lamina X.

Both ICV and intrathecal injections of 5,7 DHT caused a 92% reduction in 5-HT and 5-HT IAA levels in the lumbosacral spinal cord. No significant change in 5-HT or 5-HT IAA levels were seen in the medulla or hypothalamus after intrathecal 5,7 DHT. However, ICV injection of 5,7 DHT did reduce 5-HT and 5-HT IAA levels in both the medulla (by 48%) and hypothalamus (by 40%). These data suggest that ICV injections damaged both descending and ascending 5-HT containing pathways, whereas the intrathecal injections reduced

TABLE 1

EFFECT OF 5,7 DHT TREATMENT ON NORADRENALINE (NA) CONCENTRATIONS

	NA Concentrations (ng/mg Protein)	
	Vehicle	5,7 DHT
Spinal cord	11.4 ± 0.81	13.1 ± 2.84
Medulla	15.9 ± 2.64	13.8 ± 2.36
Hypothalamus	13.2 ± 2.10	15.5 ± 2.54

Values are mean ± SE.
n = 9–12.

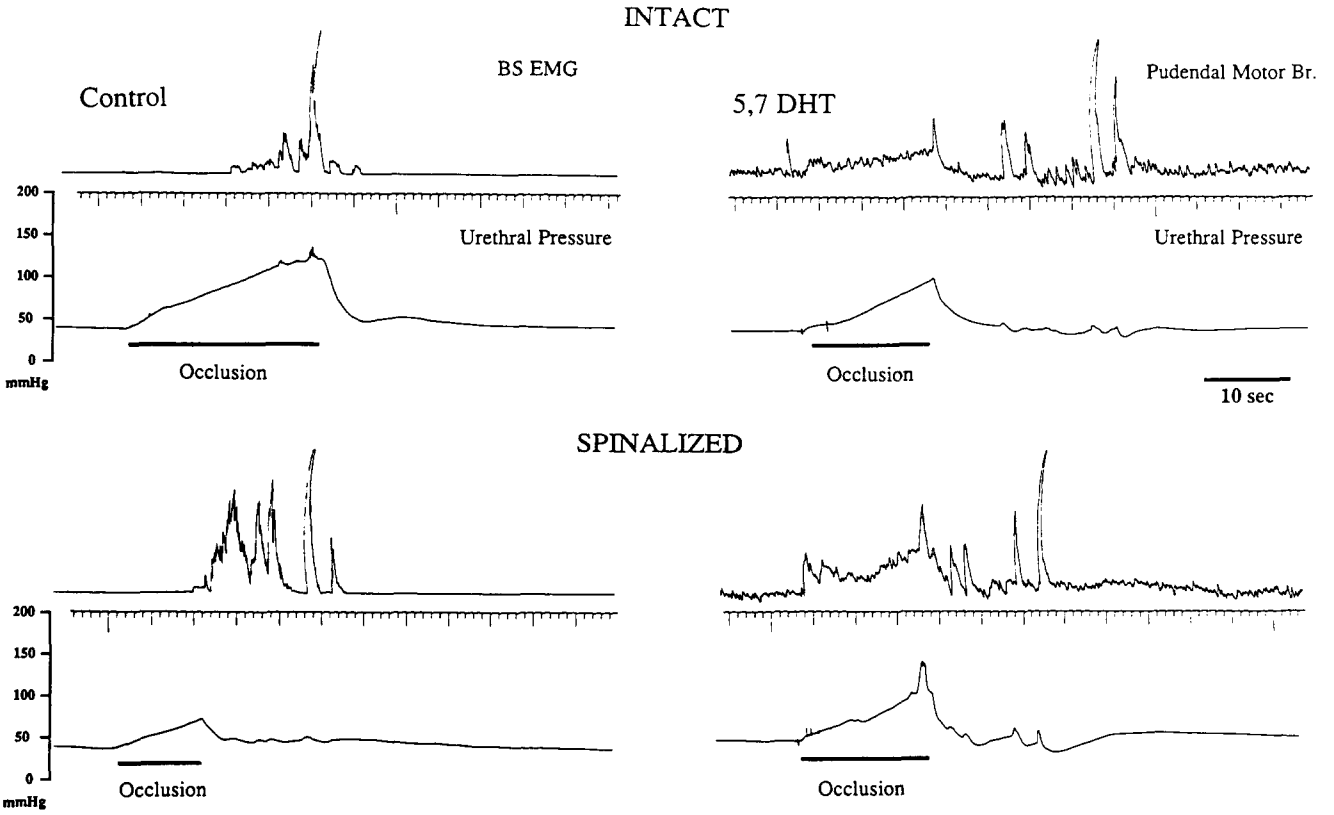

FIG. 2. Polygraph tracings illustrating the effects of intrathecal 5,7 DHT and spinal cord transections on the UG reflex. Distension of the urethra was accomplished by saline infusion and brief occlusion of the urethral meatus. The UG reflex consists of rhythmic firing of the bulbospongiosus EMG (BS EMG) and pudendal motor branch (rectified and integrated signals with a 200 ms time constant) on release of the occlusion. In the intact control (top panel) the UG reflex cannot be evoked; however, pretreatment with 5,7 DHT exposed the UG reflex (top panel). After spinal cord transection at C1 (spinalized) the UG reflex is present in both control and 5,7 DHT-treated rats (bottom panels).

serotonin levels only in descending pathways. All rats were pretreated with desimipramine, and noradrenaline concentrations were not affected by 5,7 DHT treatment. Thus, destruction of descending 5-HT pathways were sufficient to remove the supraspinal inhibition of the UG reflex.

Previous neurotoxic lesion studies suggested that inhibition of sexual function by 5-HT was mediated by ascending 5-HT pathways (19,28). However, the effects produced by 5,7 DHT could also be explained by the destruction of descending 5-HT pathways. Intracerebral injection of 5,7 DHT resulted in an increase in the number of ejaculations in animals whose sexual performance was compromised by castration (19). Intrathecal injection of 5,7 DHT reduced intromission latency in rats whose ^{14}C 5-HT binding was suppressed by 35% (14). Electrolytic lesions of the dorsal raphe produced an increase in intromission latency and a decrease in intromission frequency and a decrease in refractory period. The decrease in refractory period was the most significant effect, suggesting that serotonergic systems in the midbrain normally exert an inhibitory influence over the resumption of mating (28). These authors then injected 5,7 DHT into the dorsal raphe and found a decrease in ejaculatory latency as well as a decrease in refractory period, again suggesting an inhibitory role of 5-HT on sexual function. However, the 5,7 DHT injections were very large (4 μl) and no HPLC or immunohistochemical data was presented that would have indicated which 5-HT neurons may have been damaged. These injections may have spread to medullary 5-HT neurons, and the reduction in ejaculatory latency seen after 5,7 DHT injections and not after electrolytic lesions may have been due to destruction of descending 5-HT systems. Because both 5,7 DHT injections and electrolytic lesions decreased the refractory period, this change may be due to destruction of ascending 5-HT systems.

Very little work has been done on sexual reflexes in species other than the rat. Genital stimulation of the penis in dogs elicits erections and ejaculation (18,30). Systemic administration of 5-hydroxytryptophan and Ro4-4602, a peripheral decarboxylase inhibitor, inhibited ejaculation while erection was maintained (18). Spinal 5-HT and 5-HT IAA levels were increased in parallel with the inhibition of ejaculation (30). Rapid ejaculation can result in unsatisfactory sex. Clomipramine inhibits the reuptake of 5-HT, leading to higher synaptic levels of the neurotransmitter. Humans treated with low doses of clomipramine were reported to be able to delay ejaculation, resulting in more satisfactory performance (13). These studies suggest that 5-HT exerts an inhibition over ejaculatory responses in dogs and humans.

The present study reports that 5,7 DHT treatment overcomes the supraspinal inhibition of the UG reflex. The pressure thresholds required to elicit the reflex and the latency to onset of the UG reflex were significantly greater with 5,7 DHT treatment than after spinal cord transections. We offer a number of suggestions that may explain these results. Compensatory mechanisms, that have not yet been elucidated, may have

TABLE 2

EFFECTS OF 5,7 DHT ON THE URETHROGENITAL REFLEXES BEFORE AND AFTER SPINAL CORD TRANSECTION (SCT)

	n	Threshold (mmHg)	Latency (s)	Duration (s)	Bursts (Number)
ICV					
Before SCT: 5,7 DHT	6	89 ± 16.9*	9 ± 3.3*	38 ± 10.7*	6 ± 1.7
After SCT: 5,7 DHT	7	23 ± 2.1	2 ± 0.5	11 ± 0.8	5 ± 0.4
After SCT: Control	6	21 ± 4.5	0.3 ± 0.2	12 ± 0.8	5 ± 0.4
INTRATHECAL					
Before SCT: 5,7 DHT	5	72 ± 12.7*	12 ± 4.9*	12 ± 4.8	3 ± 0.9
After SCT: 5,7 DHT	10	23 ± 4.1	2 ± 1.0	13 ± 1.3	4 ± 0.4
After SCT: Control	10	24 ± 3.8	1 ± 0.4	15 ± 2.0	5 ± 1.0

Data are presented as mean ± SE for the given number of rats.

Fifty percent (5 out of 10) of the intrathecal 5,7 DHT-administered rats and 86% (6 out of 7) of the ICV 5,7 DHT-administered rats showed the UG reflex prior to spinal cord transection (SCT), only the responders are represented in the table.

*Represents a significant difference ANOVA (see text for *F* values). There were no significant differences between the 5,7 DHT and control group after SCT.

developed during the 10–12-day survival period. The concentration of spinal 5-HT was significantly reduced (by 92%) but not completely abolished. In addition, remaining 5-HT receptors in the spinal cord may be supersensitive to 5-HT. Alterations in 5-HT_{1A} and 5-HT_{1B} binding in the spinal cord, were shown to increase 7–14 days after 5,7 DHT treatment, suggesting upregulation of postsynaptic binding sites (6). Denervation supersenstivity and regrowth of damaged fibers have also been documented after neurotoxin treatment (11). In addition, supersensitivity to 5-HT has been shown following depletion of 5-HT by 5,7 DHT (32).

Radioligand binding studies have identified 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_2, and 5-HT_3 receptor subtypes in the brain and spinal cord (4,7,17,22). Several studies have investigated the effects of 5-HT receptor subtypes on sexual behavior and sexual reflexes, and both excitatory and inhibitory effects have been reported (2,9,20,27,33). The site of action of the administered 5-HT agonists and the animal models used vary, leading to some debate as to the exact role of each receptor subtype. 5-HT may not be the only neurotransmitter involved in erectile and ejaculatory control. Neuropeptides such as substance P (SP) and thyrotropin releasing hormone (TRH) are colocalized with 5-HT in nPGi spinally projecting neurons, for example (16,31), and have been shown to affect sexual behavior. Because destruction of the bulbospinal serotonergic neurons also reduced SP and TRH levels in the spinal cord, destruction of the 5-HT neurons by 5,7 DHT would also deplete SP and TRH levels in the spinal cord (12).

In conclusion, the present study has shown that administration of the neurotoxin 5,7 DHT depletes 5-HT and 5-HT IAA in descending pathways and disinhibits the UG reflex. These data provide further support for an inhibitory effect of 5-HT on spinal sexual reflexes. The receptor subtype and the role of substances coreleased with 5-HT in the spinal cord to inhibit the UG reflex remain to be elucidated.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Jon Levine for the use of his HPLC supported by HD 28048 and Marsha List for excellent technical support. This work was supported by NIH grant numbers NS29420 awarded to Lesley Marson and NS17489 awarded to Kevin E. McKenna.

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