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5-HT Agonist Induced Analgesia Modulated by Central But Not Peripheral Noradrenaline Depletion in Rats

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With 4 Figures

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Summary

The antinociceptive effect elicited by the 5-hydroxytryptamine (5-HT) agonist 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) was reversed or blocked in animals which had previously sustained severe spinal noradrenaline (NA) depletion via either systemic N-2-chlorethyl-N-ethyl-2-bromobenzylamine hydrochloride (DSP 4), neonatal 6-hydroxydopamine (neon. 6-OHDA), or intrathecal 6-OHDA treatment. Biochemical analysis of the lumbar spinal cord samples confirmed severe central NA depletions. Animals were tested with nondamaging heat pain (tail-flick test, hot-plate test) and electric footshock titration to determine the amount of antinociception or nociception. Peripheral NA depletion following intravenous (i.v.) 6-OHDA injection to adult rats had no effect on the antinociception induced by 5-MeODMT, but did cause severe NA depletions in the left heart atrium. These results suggest a modulatory effect of central and not peripheral noradrenergic system upon 5-HT agonist induced analgesia, and also give evidence that this effect is spinally mediated.

Key words: Analgesia, DSP 4, 6-hydroxydopamine (6-OHDA), 5-hydroxytryptamine (5-HT), 5-methoxy-N, N-dimethyltryptamine (5-MeODMT), noradrenaline (NA).

Introduction

Nociceptive afferent inputs are modulated by descending inhibitory monoaminergic pathways which are in part noradrenergic (Reddy and Yaksh, 1980). Nociceptive thresholds also increase when noradrenaline (NA) is administered intrathecally (Howe *et al.*, 1983; Howe and Yaksh, 1982). The experimental data, however, is inconsistent regarding the modulatory effect of central and/or peripheral NA depletion upon the processing of nociceptive transmission. Analgesia has been reported after lesions of the locus coeruleus (Bodnar *et al.*,1978), while lesions of the sympathetic system produce either no effect (Ashford *et al.*, 1976; Fibiger and Mason, 1978; Mason and Fibiger, 1979; Mason *et al.*, 1978), an inhibitory effect (Heller *et al.*, 1968; Paalzow, 1974; Spaulding *et al.*, 1979), or an excicatory role in pain processes (Coderre *et al.*, 1984; Wall *et al.*, 1979). Other studies report a tonic influence of descending monoaminergic pathways based upon the observation that destruction of spinal monoamine terminals with 6-hydroxydopamine (6-OHDA) significantly decreases nociceptive thresholds (Proudfit and Yaksh, 1980).

Systemic administration of N-2-chlorethyl-N-ethyl-2-bromobenzylamine hydrochloride (DSP 4) causes a sustained depletion of endogenous NA concentrations in several regions including the spinal cord which have terminals of neurons originating in the locus coeruleus (Archer *et al.*, 1984; Jaim-Etcheverry and Zieher, 1980; Jonsson *et al.*, 1981). Peripheral effects of the drug though, dissipate within seven to ten days (Archer *et al.*, 1984). Repeated injections of 6-OHDA to neonatal rat pups cause selective and permanent destruction of the locus coeruleus NA system and the peripheral NA system (Clark *et al.*, 1972; Taylor *et al.*, 1972), whereas systemically administered 6-OHDA to adult rats causes only peripheral NA stores to be destroyed (Cass *et al.*, 1960; Kostezewa and Jacobowitz, 1974).

Descending 5-hydroxytryptamine (5 HT) pathways originate in the raphe magnus nuclei (Dahlström and Fuxe, 1965). 5-HT has been implicated in the modulation of spinal nociceptive transmission (Fields *et al.*, 1977; Oliveras *et al.*, 1975), but the precise mechanism and status of this analgesia is as yet unknown. For example, methysergide failed to block the descending inhibition evoked from the raphe magnus nuclei unless given intravenously at 2 mg/kg (Griersmith *et al.*, 1981). Hall *et al.*, (1981) failed to alter the tonic inhibition of serotonergic neurons with midline medullary lesions while Soja and Sinclair (1980) failed to observe an inhibition of descending neurons after p-chlorophenylalanine, suggesting descending 5-HT

systems are not involved (for a recent review see Roberts, 1984). In view of the recently reported interaction (Archer *et al.*, 1985; Minor *et al.*, 1985) between the noradrenergic and serotonergic systems, the present investigation was undertaken to determine the relative importance of central and/or peripheral noradrenaline depletion upon baseline nociceptive responses and the analgesic effect of the 5-HT agonist, 5-methoxy-N, N-dimethyltryptamine (5-MeODMT). 5-MeODMT is a direct acting 5-HT agonist (Andén *et al.*, 1971; Bradley and Briggs, 1974; Fuxe *et al.*, 1972) reported to elicit nociceptive effects when administered in low doses and antinociception when administered in high doses (Berge *et al.*, 1980). In the experiments described below a standard 1 mg/kg dose of 5-MeODMT was administered subcutaneously, which causes a consistent analgesic effect in rats (Archer *et al.*, 1985).

Materials and Methods

The subjects were male Sprague-Dawley rats weighing 350—400 g (ALAB, Sollentuna, Sweden). They were housed 4 or 5 animals to a cage, with free access to food and water, on sawdust bedding material. A twelve-hour light/dark schedule was maintained (lights on at 0600—1800 hours). Nociceptive testing was carried out during the hours of light from 0800 to 1500 hours.

The 6-OHDA hydrobromide (Sigma) was dissolved in 0.9% saline with 0.2 mg/ml ascorbic acid antioxidant and injected at a dose of 100 μg/gm subcutaneously (s.c.), to neonatal rat pups on days 1, 3, 5, 7, 9, and 11 after birth. To adults rats 6-OHDA hydrobromide (Sigma) was injected intravenously (i.v.) at a dose of 2×50 mg/kg, two weeks and one week prior to nociceptive testing. DSP 4 (Astra Läkemedel AB, Sweden) was dissolved in 0.9% saline and injected i.p. at a dose of 2×50 mg/kg to mature rats two weeks and one week prior to nociceptive testing. In the fourth experiment, NA and 5-HT were differentially depleted in the spinal cord by intrathecal administration of either 6-OHDA or 5,7-dihydroxytryptamine (5,7-DHT). Surgery was performed under Brietal anestesia (40 mg/kg, i.p.). A polyethylene catheter (PE 10; Clay Adams), previously stretched to double its length, was inserted 8.5 cm into the subarachnoidal space through a slit in the atlanto-occipital membrane so that the caudal end of the tube was located in the region of the lumbar enlargement (Yaksh and Rudy, 1976). 6-OHDA (20 μg in 10 μl vehicle, 0.2% ascorbic acid in 0.9% saline) was injected over one minutes 10 minutes after systemic administration of pargyline (20 mg/kg, i.p.) and the catheter was removed after 5 minutes. Sham operated rats were treated identically except that vehicle only was injected. 5,7-DHT (20 μg in 10 μl 0.9% saline) was injected over a period of 30 seconds, 30 minutes after systemic administration of DMI (20 mg/kg i.p.) and the catheter was

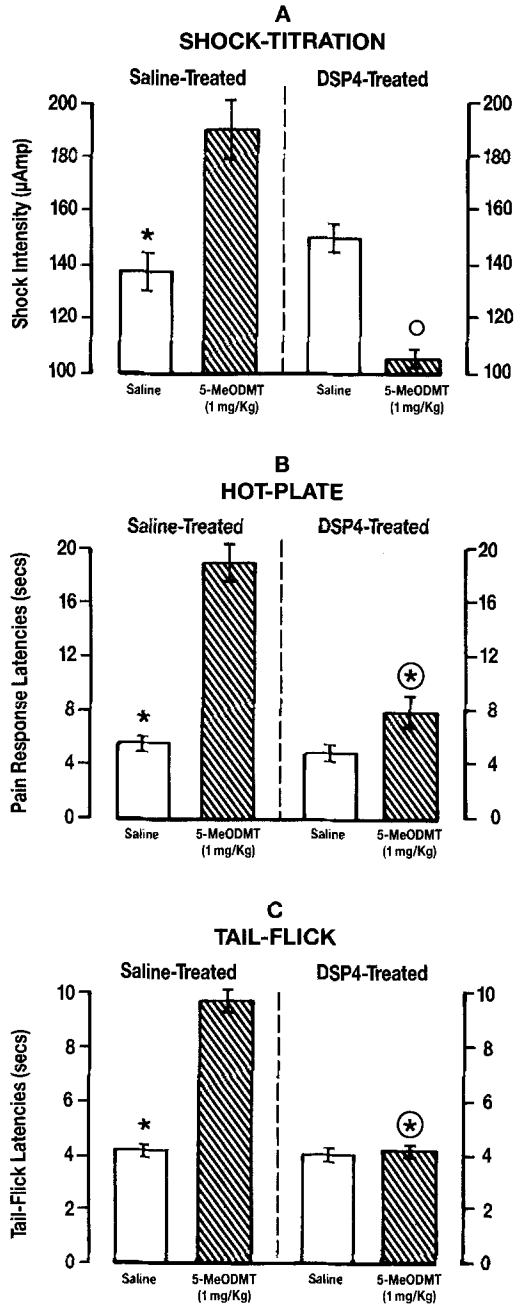
removed after 5 minutes. Any rats demonstrating signs of motor impairment twenty-four hours after surgery were discarded from the experiment. 5-MeODMT (Regis Chemical Co., USA) was dissolved in 0.9% saline, after which a dose of 1 mg/kg was injected subcutaneously (s.c.) 10 minutes prior to nociceptive testing.

Tail-flick latencies were determined using an IITC INC. Mod. 33 Analgesia-Meter. Two pre-tests were performed on each animal after which 5-MeODMT or saline and the test was given 10 minutes later. For the tail-flick test one or two tests were performed. During testing, animals were restrained in a plastic tube to which they had been previously adapted two times (20 minutes) a day for three days. Antinociceptive testing consisted of a beam of light focused 1–2 cm from the tip of the tail and the time interval from the onset of the heat stimulus to the flick of the tail being recorded. A mandatory cut off time of 15 seconds was imposed if the animal did not respond.

Hot-plate testing was conducted with an IITC INC. Mod. 35 Analgesia-Meter which was heated and maintained at 58 ±2 C. Animals were confined to the hot plate of the apparatus by a plexiglass chamber measuring 27 × 26 × 28 cm. Adaption to the apparatus was accomplished through a one minute pre-exposure period prior to nociceptive testing. The time interval from when the animals were placed on the surface of the hot-plate, to a vigorous shaking or licking of the hind paws was recorded. A mandatory cut-off time of 20 seconds was imposed if the animals did not respond.

Shock-titration was performed in a box (25 × 26 × 30 cm, Campden Instruments Ltd., London), wired to present scrambled foot shock at varying μA intensities. The test box was designed so that concomitant upon presentation of a shock any sudden movement of the animal was translated into a voltage signal (Gage *et al.*, 1980; Turner and Gage, 1982). This was accomplished by the use of four strain gauges located under each of the corners. Shocks (0.75 seconds) were delivered to the grid floor by a shock generator and shock scrambler (Model 521/c and 521/e, Campden Instruments Ltd., London) at the 50, 75, 100, 125, 150, 175, 200, 250, 275, 300 μA intensities. After a three minute habituation to the box, shock presentation was given at the 150 μA level and then presented in a higher or lower intensity depending on the animals nonresponse or response.

Fig. 1. The reversal of 5-MeODMT-induced analgesia in the shock-titration test *A* and the blockade of 5-MeODMT-induced analgesia in the hot-plate *B* and tail-flick *C* tests following pretreatment with the NA neurotoxin, DSP 4. Acute 5-MeODMT (1 mg/kg) was injected 10 minutes prior to testing. DSP 4 (50 mg/kg, i.p.) was injected on two occasions three and four weeks before testing. For statistical analysis, the acute 5-MeODMT groups were compared to the appropriate acute saline groups within each pretreatment condition and to the respective 5-HeODHT groups in the other pretreatment condition, using the nonparametric Mann-Whitney U-test (46). Values are expressed as medians ± quartiles. * vs 5-MeODMT group (same pretreatment condition), O vs Saline group (same pretreatment condition) as well as the 5-MeODMT group of the control condition. ⊛ vs 5-MeODMT group (control condition)


A
SHOCK-TITRATION
Saline-Treated
DSP4-Treated
Shock Intensity (µAmp)
200
180
160
140
120
100
Saline
5-MeODMT (1 mg/Kg)
Saline
5-MeODMT (1 mg/Kg)
B
HOT-PLATE
Saline-Treated
DSP4-Treated
Pain Response Latencies (secs)
20
16
12
8
4
0
Saline
5-MeODMT (1 mg/Kg)
Saline
5-MeODMT (1 mg/Kg)
C
TAIL-FLICK
Saline-Treated
DSP4-Treated
Tail-Flick Latencies (secs)
10
8
6
4
2
0
Saline
5-MeODMT (1 mg/Kg)
Saline
5-MeODMT (1 mg/Kg)

Catecholamine Assay

Endogenous catecholamines were determined using high pressure liquid chromatography with an electrochemical detector according to Keller *et al.* (1980). Endogenous 5-hydroxytryptamine was determined according to Ponzio and Jonsson (1979).

Statistics

Pairwise differences between groups were computed using the Mann-Whitney U-test (Siegel, 1974). The 2% level of significance was maintained throughout.

Results

Experiment 1

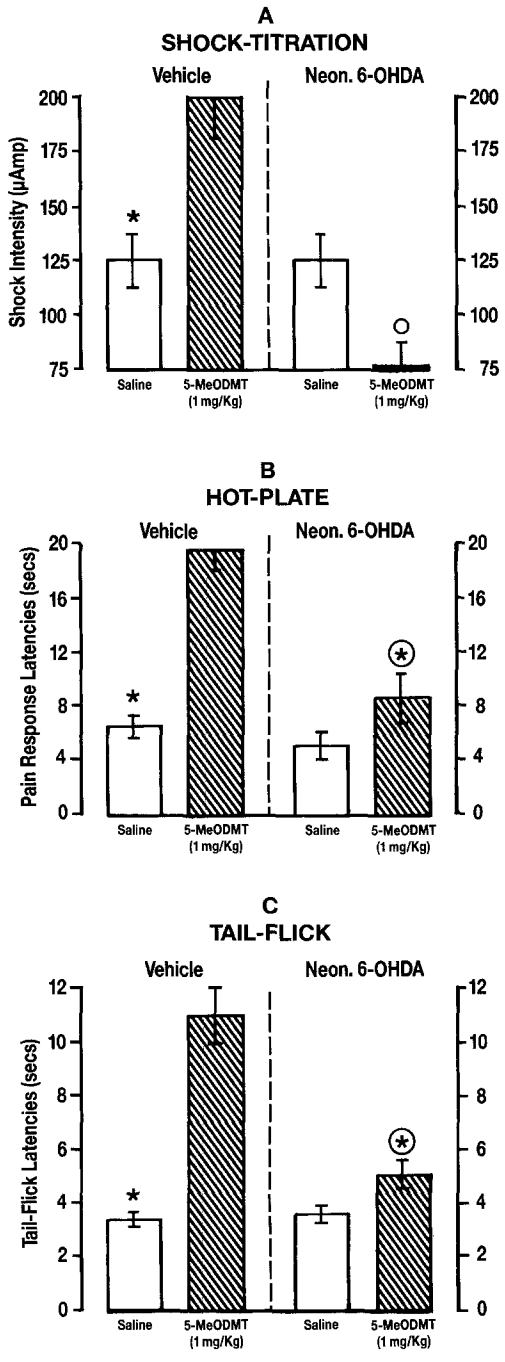
DSP 4-treated (see above) and saline-treated groups (n = 16) were administered either 5-MeODMT (1 mg/kg, s.c., n = 8) or saline (n = 8) 10 minutes prior to nociception testing. The tail-flick, hot-plate and shock titration tests were performed as outlined above.

5-MeODMT(1 mg/kg) induced a significant and considerable analgesic effect in the saline-treated rats in all three tests of nociception. The analgesic effect of 5-MeODMT in the shock titration test was reversed to an hyperalgesia in the DSP 4-treated rats, i.e. for the DSP 4-treated rats the shock threshold of the acute 5-MeODMT group was significantly lower than for the acute saline group. The analgesic effects of 5-MeODMT in the hot-plate and tail-flick tests were blocked completely by DSP 4 treatment.

Experiment 2

Neonatal 6-OHDA treated (see above) and saline-treated groups (n = 15 and 16, respectively) were treated with either 5-MeODMT (1 mg/kg, s.c., n = 8) or saline (n = 7 or 8) 10 minutes prior to nociception testing.

Fig. 2. The reversal of 5-MeODMT-induced analgesia in the shock-titration test *A* and the blockade of 5-MeODMT-induced analgesia in the hot-plate *B* and tail-flick *C* tests following neonatal 6-OHDA treatment. Acute 5-MeODMT was injected 10 minutes prior to testing. 6-OHDA 100 μg/gm, i.p.) was injected on Days 1, 3, 5, 7, 9 and 11 after birth. Statistical analysis was performed as above. Values are expressed as medians ± quartiles. * vs 5-MeODMT group (same pretreatment condition), O vs Saline group (same pretreatment condition) as well as the 5-MeODMT group of the control condition. ⊛ vs 5-MeODMT group (control condition)


A
SHOCK-TITRATION
Vehicle
Neon. 6-OHDA
Shock Intensity (μAmp)
200
175
150
125
100
75
Saline
5-MeODMT (1 mg/Kg)
Saline
5-MeODMT (1 mg/Kg)
B
HOT-PLATE
Vehicle
Neon. 6-OHDA
Pain Response Latencies (secs)
20
16
12
8
4
0
Saline
5-MeODMT (1 mg/Kg)
Saline
5-MeODMT (1 mg/Kg)
C
TAIL-FLICK
Vehicle
Neon. 6-OHDA
Tail-Flick Latencies (secs)
12
10
8
6
4
2
0
Saline
5-MeODMT (1 mg/Kg)
Saline
5-MeODMT (1 mg/Kg)

As in Experiment 1, 5-MeODMT (1 mg:kg) caused significant and reliable analgesic effects in the vehicle-treated rats in all three tests of nociception (see Fig. 2 A, 2 B and 2 C, left-hand panel). Also, as in Experiment I, the analgesic effect of 5-MeODMT in the shock titration test was reversed to an hyperalgesia (see Fig. 2 a, right-hand panel) in neonatal 6-OHDA treated rats, with shock threshold levels of the acute 5-MeODMT group that were significantly lower than those of the acute saline group. The analgesic effects of 5-MeODMT in the hot-plate and tail-flick tests were blocked completely by the neonatal 6-OHDA treatment (see Fig. 2 B and 2 C, right-hand panel).

Experiment 3

Adult 6-OHDA treated (see above) and saline-treated groups ($n = 16$ and 15, respectively) were injected either 5-MeODMT (1 mg/kg, s.c., $n = 8$) or saline ($n = 7$ or 8) 15 minutes prior to nociception testing.

The systemic 6-OHDA (2×50 mg/kg, i.v.) treatment of adult rats did not cause any consistent blockade of 5-MeODMT-induced analgesia. Thus, a considerable degree of analgesia was obtained as a result of acute 5-MeODMT (1 mg/kg) treatment with all three nociceptive tests for both the vehicle treated rats (see Fig. 3 A, 3 B and 3 C, left-hand panel) and the adult 6-OHDA treated rats (see3 A, 3 B and 3 C, right-hand panel). In the hot-plate test only, the 5-MeODMT group that was administered 6-OHDA showed a significantly lower pain response latency than the vehicle-injected 5-MeODMT group at the 5% level of significance.

Experiment 4

6-OHDA, 5,7-DHT and sham operated groups ($n = 15$, 15, 14, respectively) were administered either 5-MeODMT (1 mg/kg, s.c.) or saline, 10 minutes prior to nociception testing.

Intrathecal 6-OHDA treatment reversed the analgesic effects of acute 5-MeODMT in the shock titration measure of pain sensitivity

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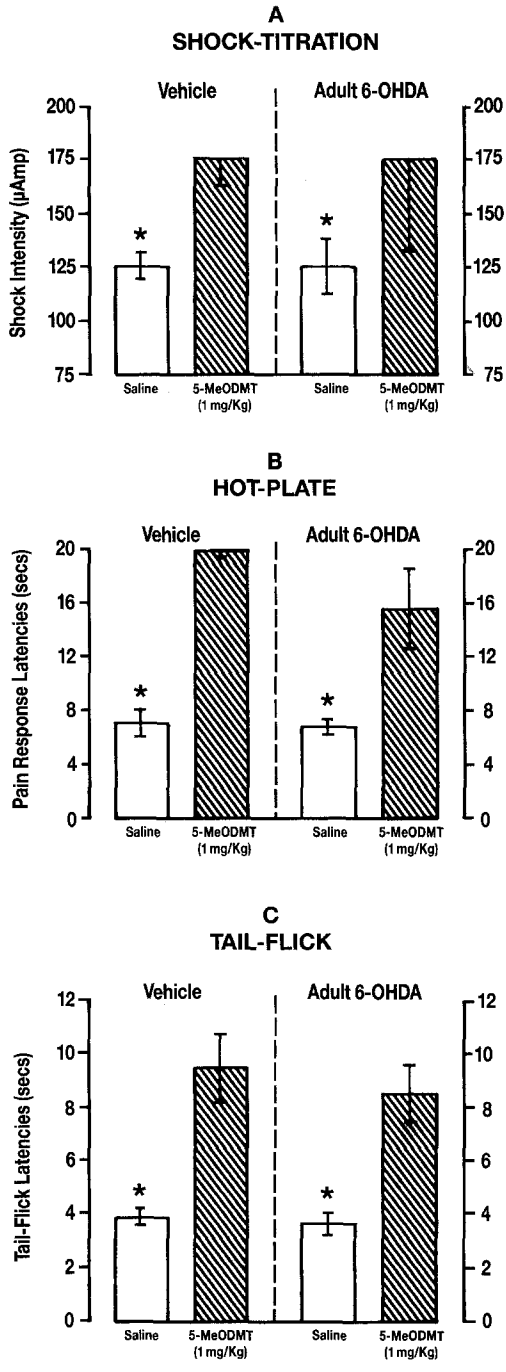
Fig. 3. Lack of reversal or blockade of 5-MeODMT-induced analgesia in the shock-titration *A*, tail-flick *B* and hot-plate *C* tests, following systemic administration of 6-OHDA to adult rats. Acute 5-MeODMT (1 mg/kg) was injected 10 minutes before testing. Systemic 6-OHDA (2×50 mg/kg, i.v.) was administered on two occasions and days before testing. Statistical analysis was performed as above. Values are expressed as medians $\pm$ quartiles. * vs 5-MeODMT group (same pretreatment condition)

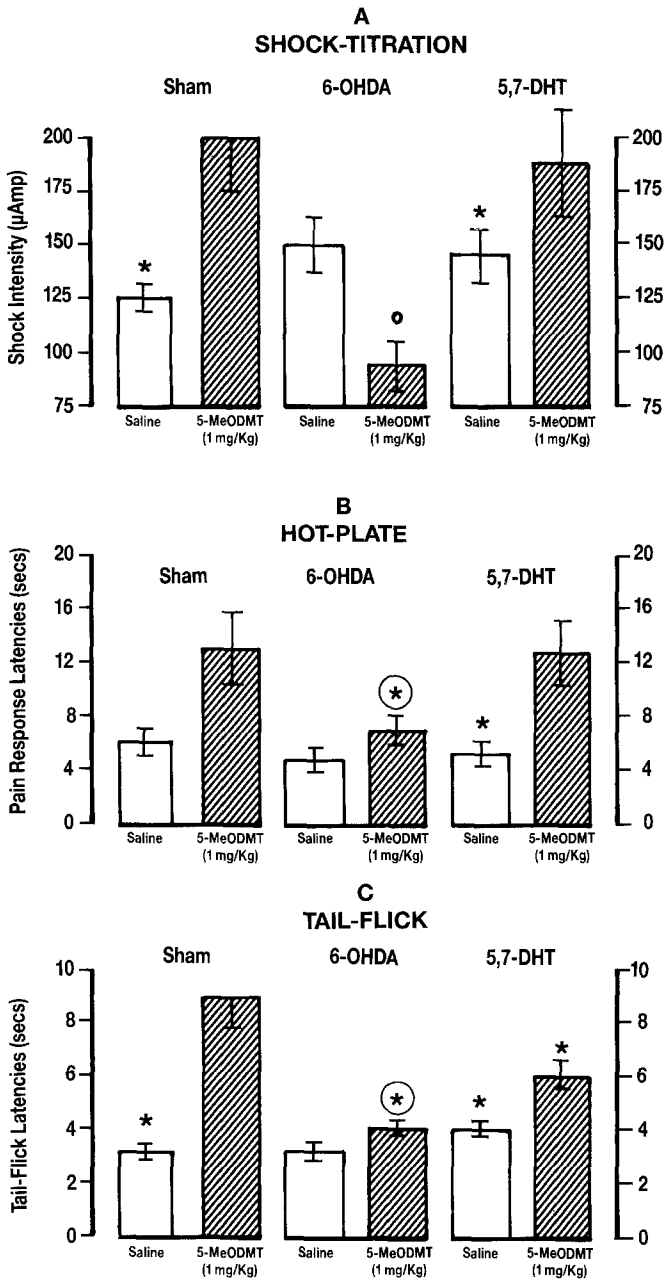

A
SHOCK-TITRATION
Vehicle
Adult 6-OHDA
Shock Intensity (μAmp)
200
175
150
125
100
75
Saline
5-MeODMT (1 mg/Kg)
B
HOT-PLATE
Pain Response Latencies (secs)
20
16
12
8
4
0
C
TAIL-FLICK
Tail-Flick Latencies (secs)
12
10
8
6
4
2
0

to an hyperalgesia (see Fig. 4 A), as NA depletion did in the first two experiments. For the hot-plate and tail-flick tests, the analgesic effect of 5-MeODMT was blocked completely (i.e. the acute 5-MeODMT group in the 6-OHDA condition did not differ from its PRE-Test threshold) by intrathecal administration of 6-OHDA (see Fig. 4 B and 4 C). For the tail-flick test only, intrathecal administration of 5,7-DHT caused a partial blockade of the acute 5-MeODMT induced analgesia (see Fig. 4 C). This may have been due to the small, but significant, NA depletion (79% of SHAM values) caused by 5,7-DHT. Intrathecal 6-OHDA, by itself (acute saline), raised the pain threshold in the shock titration test slightly, but significantly ($p < 0.05$), but since 6-OHDA treatment tended to lower pain thresholds in the hot-plate and tail-flick tests no consistent conclusion can be drawn.

Biochemical Analysis

The catecholamine assays of the spinal cord and left heart atrium regions from the neonatal 6-OHDA treated rats and adult 6-OHDA treated rats used in Experiments 2 and 3 are presented in Table 1. Neonatal 6-OHDA treatment caused a severe depletion of spinal NA (1% and 9% control values) and to a lesser extent NA concentrations in the atria (71% and 61% of control values), whereas dopamine (DA) was depleted (around 50—60% of controls) almost equally in both regions. Adult 6-OHDA did not cause any spinal NA or DA depletion at all but did cause severe peripheral NA depletions (5% and 8% of control values) and slightly less severe peripheral DA depletions (13% and 16% of control values) in the left heart atrium. Intrathecal 6-OHDA administration caused a severe depletion of NA in the lumbar region of the spinal cord (1% of control values) but no depletion of 5-HT (102% of control values). Intrathecal 5,7-DHT administration caused a drastic 5-HT depletion (4% of control values) and only a slight, but significant, depletion of NA (79% of control values). Monoamine assays of the spinal cords of the rats used in Experiment 4 are presented in table 2.

Fig. 4. The reversal of 5-MeODMT-induced analgesia in the shock titration test *A* and the blockade of 5-MeODMT-induced analgesia in the hot-plate *B* and tail-flick *C* tests following intrathecal pretreatment with 6-OHDA. Acute 5-MeODMT (1 mg/kg) was injected 10 minutes prior to testing. Intrathecal 6-OHDA or 5,7-DHT were injected four weeks before testing. Statistical analysis was performed as above. Values are expressed as medians ± quartiles. * vs 5-MeODMT group (same pretreatment condition), O vs Saline group (same pretreatment condition) as well as the 5-MeODMT group of the control condition. ⊛ vs 5-MeODMT group (SHAM condition)


A
SHOCK-TITRATION
Sham
6-OHDA
5,7-DHT
Shock Intensity (μAmp)
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5-MeODMT (1 mg/Kg)
B
HOT-PLATE
Pain Response Latencies (secs)
20
16
12
8
4
0
C
TAIL-FLICK
Tail-Flick Latencies (secs)
10
8
6
4
2
0

Table 1. *Changes in noradrenaline (NA) and dopamine (DA) concentrations in the spinal cord and atria of adult rats treated with 6-hydroxydopamine (6-OHDA) either at birth or as adults. Neonatal 6-OHDA (100 μg/g) was administered on Days 1, 3, 5, 7, 9 and 11 postnatally. Adult 6-OHDA (50 mg/kg, i.v.) was administered twice 7 and 14 days before testing*

		Neon. 6-OHDA		Vehicle	
		5-MeODMT	Saline	5-MeODMT	Saline
Spinal Cord	NA	6 ± 4[a]	45 ± 49[a]	474 ± 22	520 ± 29
	(%)	(1)	(9)	(91)	
	DA	16 ± 1.5[a]	18 ± 2.5[b]	21 ± 2	26 ± 2
	(%)	(62)	(69)	(81)	
Left Heart Atrium	NA	1283 ± 173[b]	1093 ± 167[b]	1721 ± 94	1797 ± 221
	(%)	(71)	(61)	(96)	
	DA	17 ± 2[b]	13.5 ± 3.5[b]	33 ± 14	29 ± 13
	(%)	(59)	(47)	(114)	
		Adult 6-OHDA		Vehicle	
Spinal Cord	NA	483 ± 74	401 ± 30	424 ± 27	417 ± 38
	(%)	(116)	(96)	(102)	
	DA	19 ± 3	19 ± 2	17 ± 2	17 ± 1.5
	(%)	(112)	(112)	(100)	
Left Heart Atrium	NA	99 ± 26[a]	165 ± 51[a]	1717 ± 68	2084 ± 325
	(%)	(5)	(8)	(82)	
	DA	4 ± 2[a]	5 ± 2.5[a]	35 ± 6.5	31 ± 39
	(%)	(13)	(16)	(113)	

[a] $p < 0.001$, [b] $p < 0.02$, Mann-Whitney U-test
(%) = per cent change compared to saline-vehicle.
The data are expressed as μg/g;
Medians ± quartiles of 4 or 5 determinations

Table 2. *Monoamine assays (ng/g tissue) on the spinal cords of rats pretreated intrathecally with either 6-hydroxydopamine (6-OHDA), 5,7-dihydroxytryptamine (5,7-DHT) or vehicle (SHAM) five weeks before sacrifice. In each group, n = 6*

Groups	Noradrenaline	Dopamine	5-Hydroxytryptamine
SHAM	478 ± 46	26.5 ± 3.5	304 ± 27
5,7-DHT	377 ± 74[b]	24.4 ± 4	11 ± 6[a]
(%)	(79)	(91)	(4)
6-OHDA	5 ± 6[a]	23 ± 3	311 ± 28
(%)	(1)	(88)	(102)

Values are expressed as medians ± quartiles.
[a] $p < 0.001$, [b] $p < 0.02$, Mann-Whitney tests.

Discussion

The experimental results strongly suggest that central and not peripheral noradrenergic mechanisms, possibly at a spinal locus, exert a modulatory influence on the analgesic responses induced by the 5-HT agonist, 5-MeODMT. In the shock titration test, the antinociceptive effect of acutely administered 5-MeODMT (1 mg/kg) was reversed to an hyperalgesia as the result of NA depletion (DSP 4, neonatal 6-OHDA and intrathecal 6-OHDA), i.e. a significantly lowered pain threshold for flinch-jump responding in the shock box. In the tail-flick and hot-plate tests, both DSP 4, neonatal 6-OHDA and intrathecal 6-OHDA treatment abolished the antinociceptive effect elicited by 5-MeODMT while the treatment of adult animals with systemic 6-OHDA had no effect on the elevated pain thresholds resulting from acute 5-MeODMT. Neonatal 6-OHDA, DSP 4 and 6-OHDA administered to adult rats all failed to produce noticeable changes in the nociceptive threshold levels when injected in combination with acute saline. Intrathecal 5,7-DHT treatment, which attenuated 5-MeODMT induced analgesia in the tail-flick test only, caused a severe 5-HT depletion in the spinal cord and a small depletion of NA.

Systemic DSP 4 (2×50 mg/kg) causes only a transient NA depletion, lasting 4 to 7 days, in peripheral tissues whereas it causes a permanent NA depletion in central regions (Archer *et al.*, 1984). 6-OHDA administered systemically to neonatal rat pups produces both central and peripheral NA depletion although the central depletion (1% and 9% of control values) is substantially greater than the peripheral (left heart atrium) depletion (71% and 61% of control values). Intrathecal 6-OHDA treatment caused a severe depletion of spinal NA while DA and 5-HT were unaffected. Systemic 6-OHDA treatment of adult rats produced considerable NA depletion in the peripheral tissue (5% and 8% of control values) but not in the central region (116% and 96% of control values). Taken together, the antinociceptive test data in conjunction with the neurochemical data allow us to conclude that spinal NA modulates the analgesic response to systemically administered 5-MeODMT.

Previous studies have demonstrated decreased brain serotonergic activity after acute propranolol (Giarcovich and Eners, 1981). Serotonergic-catecholaminergic interactions have been shown in foot shock-induced jumping behaviour in rats (Nishikawa *et al.*, 1983), while the firing activity of 5-HT neurons in the dorsal raphe has been shown to be suppressed by alpha-adrenoceptor antagonists (Baraban and Aghajanian, 1980). Nociceptive stimuli may also acti-

vate the release of both NA and 5-HT spinally (Tyce and Yaksh, 1981), and destruction of spinal 5-HT and NA pathways elicits hyperalgesia (Howe *et al.*, 1983). In a recent series of experiments we have characterized several different 5-HT agonists that cause analgesic effects in the hot-plate, tail-flick and shock titration tests to greater or lesser degrees. These 5-HT agonists were shown to share one common property, i.e. their analgesic action was either reversed or blocked completely by DSP 4 pretreatment (Post *et al.*, 1985). Furthermore, the 5-HT antagonists only attenuated the analgesic effects of 5-MeODMT in the tail-flick test, whereas NA depletion blocked completely these effects in all three tests (Post *et al.*, 1985). This finding was supported by the result that 5-HT depletion following 5,7-dihydroxytryptamine treatment also attenuated significantly the effects of 5-MeODMT in the tail-flick test but not in the hot-plate (Archer *et al.*, 1986).

There are several possible explanations for the modulatory influence that noradrenaline exerts on the effects of 5-HT agonists in the CNS. DSP 4 or 6-OHDA causes a removal of the presynaptic NA terminals thus causing a functional postsynapic adrenoceptor supersensitivity (Dooley *et al.*, 1983). This variation of receptor sensitivity may be involved in the 5-HT agonist hyperalgesia. There is also data which supports the argument that neurotoxin-induced depletions of NA or 5-HT are accompanied by increases in the tone of the other spinal monoaminergic system (Baumgarten *et al.*, 1971). Thus, any nociceptive input to one system could be enhanced by the abolition or decrease of transmitter substance in the other system. The removal of an inhibitory NA influence could facilitate some 5-HT autoreceptor based mechanism mediated via the 5-HT agonist which may have led to the hyperalgesic state. Finally, the analgesic effects of 5-HT or a 5-HT agonist could be due to the activation of the descending noradrenergic system, the abolition of which would lead to a hyperalgesic condition.

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