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The Effects of Intracranial Administration of Hallucinogens on Operant Behavior in the Rat. II. 2,5-Dimethoxy-4-Methylamphetamine (DOM)[1]

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MOKLER, D J , K W STOUDT, L C SHERMAN AND R H RECH *The effects of intracranial administration of hallucinogens on operant behavior in the rat II 2,5-Dimethoxy-4-methylamphetamine (DOM)* PHARMACOL BIOCHEM BEHAV **28**(3) 327–334, 1987 —2,5-Dimethoxy-4-methylamphetamine (DOM) was infused into discrete brain regions of rats trained to press a bar for food reinforcement on a fixed ratio-40 (FR-40) Sites were chosen as major areas of the brain 5-hydroxytryptamine (5-HT) system the dorsal and median raphe nuclei, dorsal hippocampus, lateral habenular nuclei and the prefrontal cortex Following training in a fixed ratio-40 (FR-40) operant behavior rats were implanted with stainless steel cannulae into the brain area to be examined Bilateral cannulae were implanted for the lateral habenular nuclei, dorsal hippocampus and the prefrontal cortex Following recovery from surgery, DOM (20–300 μg) was tested on operant behavior by infusing the drug immediately before the operant session Infusion of vehicle was inactive DOM produced a dose-dependent decrease in reinforcements and a concomitant increase in 10-sec periods of non-responding (pause intervals) DOM was more potent when infused into the median raphe nucleus than following intracerebroventricular (ICV) administration DOM was less potent when infused into the dorsal raphe, prefrontal cortex or dorsal hippocampus Infusion of DOM into the lateral habenular nuclei produced a biphasic dose-response curve ED50s for increases in pause intervals were 47, 77, 92, 103, and 114 μg for infusion into the median raphe, dorsal raphe, prefrontal cortex, lateral habenulae, and dorsal hippocampus, respectively The ED50 for ICV administration in a previous study was 58 μg The effects of DOM in the lateral habenulae could be divided into two curves, one curve had an ED50 of 69 μg, whereas the other had an ED50 of 176 μg Furthermore, the dose-response curve for IP administration of DOM was shifted to the left in animals with cannulae placed into the lateral habenular nuclei No change was seen in the response to IP administration of DOM in animals cannulated in the remaining sites or in animals with ICV cannulae Therefore, the effects of DOM in disrupting operant behavior may be more critical with regard to its actions in the lateral habenulae and median raphe Nonetheless, actions at multiple brain sites probably contribute to the total behavioral effects of the drug

Intracranial Operant behavior 5-Hydroxytryptamine 2,5-Dimethoxy-4-methylamphetamine
Frontal cortex Lateral habenulae Hippocampus Raphe nuclei

THE phenethylamine hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) produces many of its effects by interactions with brain 5-HT systems [4, 5, 8, 10, 13, 15, 24, 25]. The brain sites at which DOM may be producing these effects have not been examined. Some investigations have explored the possible mechanisms and sites of action of another phenethylamine hallucinogen, mescaline. Aghajanian and co-workers [9] have reported that LSD but not mescaline by microiontophoresis inhibits all raphe cells LSD was similarly effective by IV injection while IV mescaline reduced the discharge of only a subpopulation of raphe neurons Therefore, mescaline does not mimic direct actions of LSD, but may exert some indirect actions. LSD, mescaline, dimethyltryptamine (DMT), and DOM were earlier compared by IV administration for effects on raphe unit discharge [1] DMT like LSD inhibited all raphe cells, while

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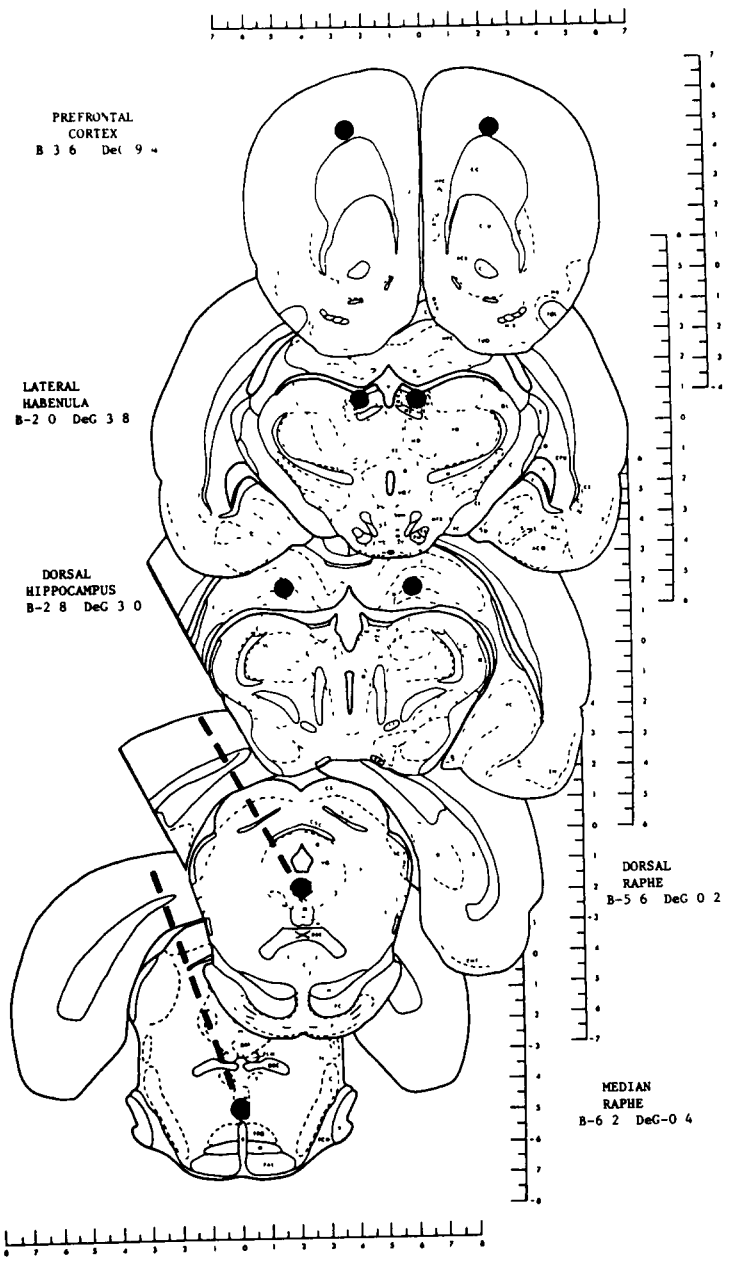

FIG 1 Sites of cannula placement (taken from [16], adapted from [20]) Guide cannulae were implanted 1 mm above the site shown The angles for dorsal and median raphe cannulae tracts are shown by a dashed line (see the Method section) B indicates A–P coordinates with reference to bregma, DeG indicates A–P coordinates with reference to DeGroot zero or interaural zero

DOM was like mescaline in decreasing the discharge of raphe cells restricted to the ventral portion of the dorsal nucleus and the dorsal aspect of the median nucleus.

The present study examines the possible sites of action of DOM by infusion of DOM into discrete brain areas of conscious rats being tested in a FR-40 schedule of operant behavior Sites were chosen based on the brain 5-HT systems. Included were the main areas of the cell bodies of ascending 5-HT neurons, the dorsal and median raphe nuclei Forebrain areas receiving major 5-HT inputs are the prefrontal cortex and the dorsal hippocampus Also examined were the lateral habenular nuclei, which contain afferents and efferents from the raphe nuclei as well as efferents from forebrain areas [3, 17, 18, 27, 28] A previous report [16] of the same design examined the actions of LSD at these same sites in these same animals. It was concluded that the activity of LSD in the dorsal raphe and prefrontal cortex may be most critical for disruption of the FR-40 operant behavioral pattern, although effects at the sites probably contribute appreciably to the overall behavioral impairments

METHOD

Animals

Male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc , Indianapolis, IN) weighing between 275–325 g at the beginning of the experiment were used Animals were housed individually in Plexiglas cages with wire tops in a room with a natural light cycle and controlled temperature and humidity. Tap water was available ad lib Rats were food-deprived to 75–80% free-feeding weights, supplemental food (Standard Lab Bloks) was given after behavioral sessions to maintain desired body weight range

Apparatus

Operant equipment consisted of 4 standard operant cages (Lehigh Valley Electronics, Lehigh Valley, PA) with one lever and food pellet dispenser. Operant cages were placed in sound attenuating chambers. The operant lever required a force of 10–15 g to operate Programming was controlled with electro-mechanical units (Lehigh Valley Electronics, Lehigh Valley, PA)

Training and Behavioral Procedures

Subjects were trained in a fixed ratio 40 (FR-40) operant paradigm using methods described previously by us [16] Animals were required to press a bar 40 times for one 45 mg food pellet (Bio-Serv, Inc , Frenchtown, NJ) Rats were placed into the operant chambers six days a week for daily 40-min sessions. Drug treatments were administered on Wednesdays and Saturdays, with the remaining days as control days. The number of reinforcers earned and the number of 10-sec periods of non-responding during the session (pause intervals) were counted for each of four 10-min periods The order of drug testing as to dose, route and multiple vehicle infusions was randomized among subjects in a counterbalanced design Data is presented as a percent of control reinforcers that were received following drug on the treatment day compared to the preceding control day's session

Stereotaxic Procedures

Guide cannulae were implanted after the animals had shown stability on the FR-40 schedule for at least a week Anesthesia was induced with administration of Equithesin (3 ml/kg, IP) Animals were placed in a standard Kopf stereotaxic apparatus Cannulae were placed according to the coordinates of Pellegrino and Cushman [22] Figure 1, taken from [16], shows the coordinates used for cannula placement; guide cannulae were placed 1 mm above these coordinates. Six animals were implanted with cannulae into the dorsal raphe, lateral habenulae and prefrontal cortex, 8 with cannulae into the median raphe, and 12 with cannulae into the dorsal hippocampus. Bilateral cannulation was performed for the lateral habenula, prefrontal cortex and dorsal hippocampus Cannulae for infusions into the dorsal or median raphe were placed using interaural zero as reference zero due to the close proximity of these sites to this point. Similarly, bregma was used as reference zero for the remaining sites This strategy has been determined by our experience and others [19] to be the most accurate for cannula placement. Cannulae aimed at the dorsal or median raphe were placed at an angle of 30 or 20 degrees from the vertical, respectively, to avoid interference with the cerebral aqueduct. Cannulae were secured to the skull with dental acrylic adhering to small screws placed into the skull

Guide cannulae were constructed of 23-gauge stainless steel hypodermic tubing (Small Parts, Inc , Miami, FL) as described previously [14,16] Guide cannulae were 10 mm in length except for those aimed at the dorsal and median raphe, which were 15 mm in length Following surgery and for the remainder of the experiment the guide cannula was occluded with a length of 0 016″ stainless steel wire, which extended 1 mm beyond the tip of the guide cannula

TABLE 1

BASELINE RESPONDING IN FR-40 BEHAVIOR OF RATS IMPLANTED WITH IC CANNULAE

Site of Cannulation	n*	Reinforcers	Pause Intervals
Dorsal Raphe	5	102 ± 15	25 ± 4
Median Raphe	8	106 ± 18	20 ± 3
Lateral Habenula	6	119 ± 19	21 ± 5
Dorsal Hippocampus	12	105 ± 8	51 ± 8†
Prefrontal Cortex	6	117 ± 5	26 ± 5

*n=number of rats in each group

†Significantly different from other areas $p<0$ 05, ANOVA, least significant differences test

Drug Infusion Procedure

Infusion cannulae were constructed from 30-gauge hypodermic needles and extended 1 mm beyond the tip of the guide cannulae The cannula was connected to PE-10 tubing (Clay-Adams, Parsippany, NJ) which, in turn, was connected to a 5 μl syringe (Hamilton Co , Reno, NV) Infusions were controlled with a Harvard Infusion Pump (Harvard Apparatus, Mills, MA) connected to a Gra-Lab Universal Timer (Gray Co , Dayton, OH) While a rat was being held under gentle hand restraint, the occluder pin was removed and the infusion cannula placed into the guide cannula The rat was put back into its home cage and DOM was infused for 1 min in a volume of 1 μl This volume was chosen since earlier pilot studies infusing smaller volumes yielded unpredictable results and lack of dose-response relationships Furthermore, older studies utilizing slow intracranial infusions of drugs indicate that the threshold volume yielding morphological and functional evidence of irreversible damage is close to 2 μl (see for review [23]) Doses examined were 20, 40, 80, 100, 120, 160, 200, 240 or 320 μg DOM IC or IP. After the infusion was completed an additional minute was allowed to pass before removal of the infusion cannulae to allow for diffusion from the site. Infusions into bilateral structures were done simultaneously, 1 μl on each side Any fluid appearing at the top of the guide cannulae as well as unusual behaviors during infusion were noted

Following completion of all behavioral experiments animals were again anesthetized with Equithesin After a surgical level of anesthesia had been reached animals were perfused with 50 ml 0 9% saline via intracardiac catheter, followed by 100 ml of 10% buffered formalin The cannula cap was then gently removed and the brain removed from the skull The brain was post-fixed in 10% formalin. Cannula placement was verified by visual inspection of cannula tracts

TABLE 2

F VALUES FOR PAUSE INTERVAL DATA

	Dose	Site	Interaction
Intracranial Administration	21 5 (3,75)†	0 44 (5,75)	0 46 (15,75)
	Time Course		
Site			
Dorsal Raphe	12 8 (5,15)†	2 56 (3,45)	0 71 (15,45)
Median Raphe	1 46 (4,19)	8 13 (3 57)†	16 2 (12,57)†
Lateral Habenula	4 17 (6,23)*	2 50 (3,69)	70 3 (18,69)†
Dorsal Hipoocampus	16 6 (6,29)†	0 50 (3,87)	57 7 (18,87)†
Prefrontal Cortex	4 8 (6,15)*	1 33 (3,45)	41 5 (18,45)†

Values represent F values for ANOVA as outlined in the Method section Numbers in parentheses indicate degrees of freedom *$p<0$ 05, †$p<0$ 01

TABLE 3

TIME-COURSE OF THE EFFECTS ON PAUSE INTERVALS OF DOM INFUSED INTO VARIOUS BRAIN REGIONS

Site	Dose (μg)*	n†	Change in Pause Intervals/10-min Period 1	2	3	4
Dorsal Raphe	80	4	17‡	20	13	14
	100	3	38§	39§	48§	32§
Median Raphe	80	4	25	27	24§	8
	100	4	33§	33§	20	20
	120	8	32§	27	22	12
Lateral Habenula	80	4	26§	30§	26§	10
	120	6	27§	36§	29§	31§
	200	4	19	21	20	22§
	240	4	35§	43§	44§	40§
Dorsal Hippocampus	80	5	15§	21§	7§	2
	160	5	26§	37§	32§	20
	200	5	36§	43§	32§	22§
Prefrontal Cortex	80	3	17	27§	22	23§
	120	2	25§	14	36§	36§
	200	5	23§	38§	28§	26§

*Though more doses were tested, lower doses with little or no effect were excluded from this table

†n=number of rats tested at that dose and site

‡Represents mean for increase in pause intervals from baseline levels produced during this 10-min period of the 40-min session

§Significantly different from infusion of vehicle into that area Two-way ANOVA, least significant difference test, $p<0$ 05

TABLE 4

ED50s FOR CHANGE IN PAUSE INTERVALS ICV VS IC ADMINISTRATION

	DOM (μg)
ICV	58* (13–83)
IC	
Dorsal Raphe	77 (60–117)
Median Raphe	47 (0–95)
Lateral Habenula	103 (29–208)
(20–120 μg)	69† (13–310)
(160–240 μg)	176‡ (136–198)
Dorsal Hippocampus	114 (74–187)
Prefrontal Cortex	92 (17–298)

*Values are ED50s for increases in pause intervals using probit analysis Values in parentheses are 95% confidence limits ICV values were taken from Mokler and Rech [14]

†ED50 calculated for lower dose range (see text)

‡ED50 calculated for higher dose range (see text)

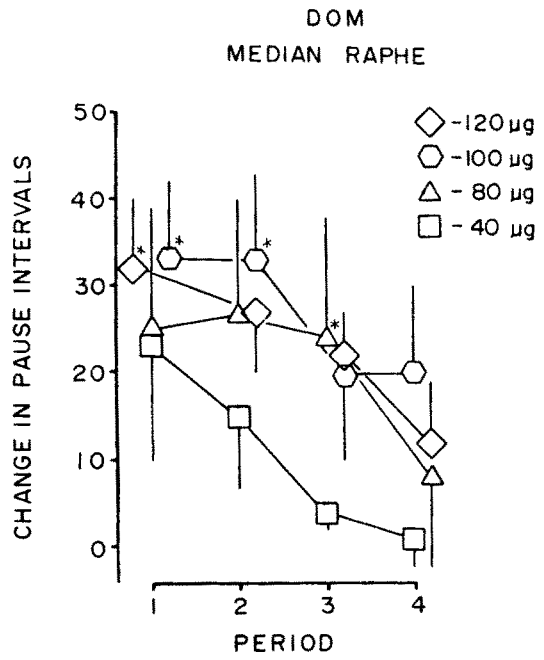

FIG 2 Time-course of the effects on pause intervals of DOM infused into the median raphe nucleus Periods represent successive 10-min segments of a 40-min operant session *$p<0$ 05, significantly different from control, least significant differences test, two-way ANOVA

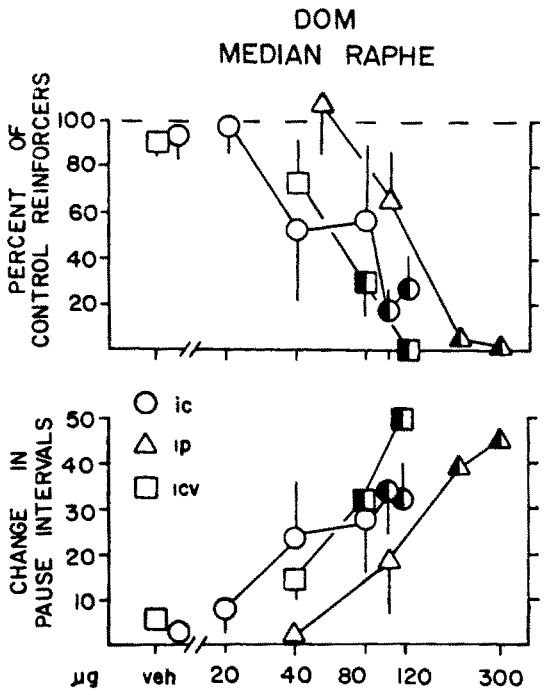

FIG 3 Peak effects of DOM following ICV administration (taken from [14]) and IC infusion into the median raphe nucleus or IP injection in the same subjects Shading of the left half of a symbol signifies a significant difference from control ($p<0$ 05, least significant differences test, one-way ANOVA)

in slices made with a freezing microtome Site of injection was determined by measuring 1 mm beyond the most ventral point of the guide cannula or, if possible, by the tract made by the infusion cannula If the cannula was placed greater than 0.5 mm from the coordinates, the data for that animal was not used

Drugs

2,5-Dimethoxy-4-methylamphetamine HCl was obtained from the National Institute on Drug Abuse. For intraperitoneal injections DOM was dissolved in 0.9% saline; injections were in a volume of 1 ml/kg and made immediately before the beginning of the session. For intracranial infusions DOM was dissolved in a solution of 2.3 mM $CaCl_2$ in sterile saline All drug weights refer to the weight of the salt

Statistics

Analysis of dose-response data for IC DOM was done using a two-way ANOVA [12]. All sites were included as well as data from intracerebroventricular administration of LSD in the same paradigm [14] in an ANOVA using dose and site as factors The time-courses of disruption were analyzed by two-way ANOVAs with time and dose as factors. The effects of IP administration in animals implanted with cannulae into various sites were analyzed using a two-way ANOVA with site and IP dose as factors. Least significant differences tests were used for post-hoc analyses. The level of significance was set at $p<0.05$ ED50s were determined using probit analysis, data were normalized using an arcsine transformation

RESULTS

Baseline response rates as determined by number of reinforcements earned in daily 40 min sessions for animals with cannulae placed into brain tissue were not significantly different for any brain areas, $F(4,32)=0$ 29 A significant difference was found in baseline pause intervals in rats implanted with cannulae into the dorsal hippocampus, $F(4,32)=4$ 48, $p<0.05$ (Table 1). Vehicle infusions were inactive at all sites examined. Infusion of DOM into various brain sites produced a disruption of behavior which was qualitatively similar to the disruption produced by IP administration, i.e , a dose-dependent decrease in reinforcers and concomitant increase in pause intervals was observed

Infusion of DOM into discrete brain regions did not produce a disruption which differed from ICV administration as far as potency relationships (Table 2). The time-course of the effects of DOM following infusion into the dorsal raphe showed peak effects during the 2nd and 3rd periods (Table 3) and the ED50 for pause intervals was 77 µg (Table 4) DOM administered into the dorsal hippocampus also produced a disruption of behavior, peak effects occurring during the second period with a slow offset (Table 3); the ED50 for pause intervals was 114 µg (Table 4). A similar response was seen following administration into the prefrontal cortex, yielding an ED50 of 92 µg.

Peak effects generally occurred during the first twenty

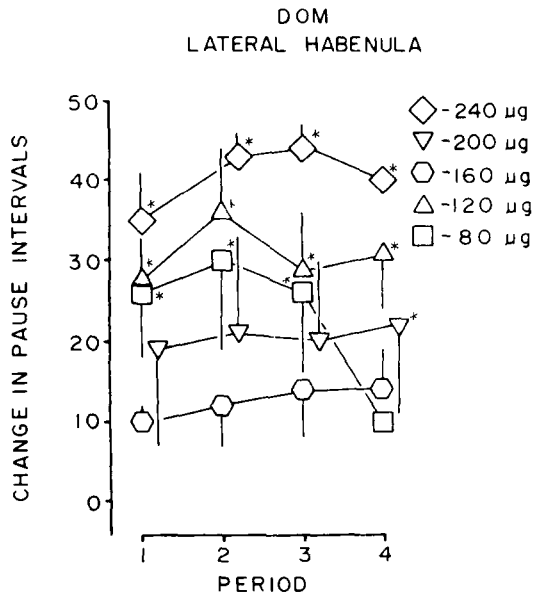

FIG 4 Time-course of the effects on pause intervals of DOM infused into the lateral habenular nuclei Periods represent successive 10-min segments of a 40-min operant session *$p<0$ 05, significantly different from control, least significant differences test, two-way ANOVA

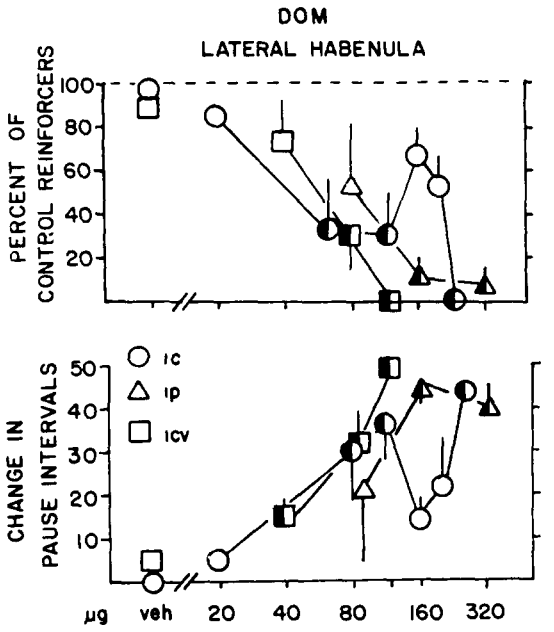

FIG 5 Peak effects of DOM following ICV administration (taken from [14]) and IC infusion into the lateral habenular nuclei or IP injection in the same subjects Conventions are the same as in Fig 3

minutes following infusion of DOM into the median raphe (Fig 2, Table 3) The dose-response pattern of the peak effect on pause intervals was similar to that response following ICV administration (Fig 3) Although the dose-response curve following median raphe infusion was shallower than that following ICV administration, there was little difference between ED50 values (47 and 58 μg for median raphe and intraventricular infusion, respectively)

Intracranial administration of DOM into the lateral habenulae produced an effect that was relatively constant for each dose level throughout the 40-min session (Fig 4) The dose-effect curve for the peak effect was found to be bimodal (Fig. 5) Low doses (20–120 μg) caused an effect which was similar to that following ICV administration, whereas higher doses (160–200 μg) produced a response curve that was shifted to the right When an overall ED50 is calculated for all data in this dose-response function, a value of 103 μg is determined (Table 4) Two separate ED50s, however, may be calculated using the two dose ranges An ED50 of 69 μg was determined for the 20–120 μg dose range and an ED50 of 176 μg for the 160–240 μg dose range

DISCUSSION

Rats with cannulae implanted into these five brain areas did not differ in reinforcers earned during baseline sessions With the exception of animals with cannulae into the hippocampus, no differences were seen in the number of pause intervals occurring during daily 40-min baseline operant sessions The increase in pause intervals in animals with hippocampal cannulae may be due to some disruption of the integrity of this brain area by the cannulae. It is not likely that this is an overall disruption of hippocampal function since larger lesions of the hippocampus generally produce an increase in response rates in an operant paradigm [26]

In each brain area studied, the time-course following infusion of DOM showed peak effects later in the session than observed after ICV infusion [14] This suggests that some redistribution from each brain area selected here was necessary for DOM to disrupt the operant behavior, diffusion from the intraventricular site to multiple brain regions of activity being expected to occur more rapidly The effects of DOM persisted throughout the 40-min session, which is consistent with the findings for IP and ICV administration of this drug [13,14]

The intracranial infusion of DOM was not significantly more potent in any brain area than following ICV administration (Table 2) Nevertheless, mean values of ED50s for DOM infused into the various sites to disrupt behavior were somewhat divergent (Table 4) Infusion of DOM into the median raphe yielded a similar potency to that after infusion into the lateral ventricles This contrasted with a trend for lower potency demonstrated by infusion of DOM into the dorsal raphe, prefrontal cortex and especially the dorsal hippocampus (Table 4) In addition, the ED50 of the lower dose range of DOM infused into the lateral habenular nuclei was close to the ED50 for ICV administration (69 and 58 μg, respectively) These data suggest that at least slight differences exist in the ability of DOM to differentially disrupt FR-40 behavior by infusion directly into the brain The potency differences after infusion of DOM into these areas of the brain is, however, much less than would be expected from infusion of a drug into a singularly active site of action Perhaps the median raphe and the lateral habenulae are slightly more critical for the disruption of behavior following administration of DOM, but other sites appear also to be important Further research along these lines could utilize simultaneous infusion of DOM into multiple brain areas to

determine if latency to onset of effect would be reduced to the ICV level.

Infusion of DOM into the lateral habenulae produced an effect that at lower doses (20–120 μg) was equipotent with ICV administration. Recent studies suggest that the habenular complex may be an important site for the integration of ascending and descending signals of the forebrain serotonergic systems. Wang and Aghajanian [28] have shown that electrical stimulation of the lateral habenula suppressed the firing of serotonergic neurons in the dorsal and median raphe nuclei. Further research has shown an important connectivity between the habenular nuclei and the raphe nuclei (see [27] for review). Although these reports support the existence of important afferent and efferent connections between the raphe nuclei and the lateral and medial habenulae, autoradiographic studies have shown only a low binding density of $5HT_1$ and $5HT_2$ receptors in the habenular nuclei [20,21]. LSD was less potent in disrupting operant behavior when infused into the lateral habenula than by ICV administration in these same animals. The specific effects of DOM or LSD on neurons in the habenular nuclei, as well as a clear understanding of anatomical and functional interconnection between habenula and raphe nuclei, remain to be established.

The biphasic dose-response curve following administration of DOM into the lateral habenular nuclei was unexpected. The pattern may relate to excitatory/inhibitory roles of DOM in the disruption of behavior following infusion into this site. Thus, low doses of DOM show a potency similar to ICV DOM in disrupting behavior. Higher doses, however, may interact in a different manner to interfere with the effect of lower doses. At the critical dose of 160 μg the area of diffusion of the drug may be sufficient to activate brain mechanisms which reverse the initial disruption, resulting in the biphasic character of the response. The placement of the cannulae was in the lateral portion of the lateral habenula. Infusion of DOM into the medial habenulae should be considered in future experiments using this approach.

The effects of DOM administered into discrete brain nuclei showed a somewhat different spectrum of effects than did infusion of LSD [16]. LSD infused into the prefrontal cortex or the dorsal raphe was as potent as or more potent than ICV administration in disrupting FR-40 responding. The ED50s were 14, 9 and 15 μg, respectively. DOM infused into these areas showed a trend for lower potencies than after ICV administration (Table 4). Median raphe infusion of DOM yielded the same potency range as for ICV administration, which was also true for lower doses of DOM infused into the lateral habenula. LSD was less potent than ICV administration when infused into these latter areas, in fact, infusion of LSD into the lateral habenula was less potent than after IP administration. Thus, the effects of LSD and DOM may involve interactions with different areas of the rat brain in spite of similarities in the overall pattern of disruption of operant behavior. Data from previous experiments support this conclusion. Reduction in brain levels of 5-HT after ICV administration of the neurotoxin 5,7-dihydroxytryptamine produced a potentiation of the effect of LSD and DOM [2, 5, 11, 29]. However, when forebrain 5-HT was depleted by administration of 5,7-DHT into the medial forebrain bundle at the level of the posterior hypothalamus, the effects of LSD were again potentiated but the effects of DOM were actually attenuated [6]. This latter treatment, for example, would spare efferents from the raphe nuclei to the habenular nuclei. This suggests that DOM may be acting on different 5-HT receptors and/or 5-HT mechanisms in different brain areas than those acted on by LSD.

Further differences between DOM and LSD have been observed in the interactions with 5-HT antagonists. Metergoline has been shown to antagonize the effects of DOM to a much greater extent than antagonism of the effects of LSD [4,13]. Similarly, the $5\text{-}HT_2$ antagonist pirenperone was more effective in blocking the effects of DOM than the effects of LSD [15]. Contrariwise, the 5-HT antagonist pizotifen was relatively more effective in attenuating the effects of LSD [13]. Thus, while the effects of these drugs are complex, evidence exists that interactions with various brain 5-HT systems is a requirement for causing this type of behavioral disruption.

Aghajanian and coworkers have shown differences between the electrophysiological effects of LSD and mescaline [1,9]. Although LSD produced a cessation in raphe cell discharge after both IV injection and microiontophoretic application onto all 5-HT neurons in the dorsal raphe, mescaline produced a more limited inhibition of raphe cell firing (ventral part of the dorsal raphe nucleus) following IV administration but not after microiontophoresis onto raphe cells.

Rats with cannulae implanted into the lateral habenulae appeared to increase in sensitivity to IP DOM, although statistical analysis of this phenomenon was not possible due to the lack of uniformity in the IP doses received by the different groups. A similar change in the IP dose-effect curve was found previously for LSD in these same animals implanted with cannulae into the dorsal raphe or the prefrontal cortex [16]. Interestingly, the dorsal raphe and the prefrontal cortex also showed the greatest sensitivity to LSD. No changes were seen in sensitivity to IP DOM in these same animals cannulated in the dorsal raphe or prefrontal cortex. Conversely, no changes were seen in the IP response to LSD in the animals with cannulae placed into the lateral habenulae [16]. The shift in the IP dose-response pattern to DOM in animals cannulated in the lateral habenular is again suggestive of the involvement of activity of DOM in this area for inducing the disruptive effects on behavior.

The relationship between the interactions of DOM with subtypes of 5-HT receptors and the findings of the present study is unclear. Past studies have shown that DOM binds preferentially to $5\text{-}HT_2$ sites as defined by (^{3}H)-ketanserin binding as the reference agonist [25]. Furthermore, the binding affinity of a number of hallucinogens for $5\text{-}HT_2$ sites in the brain correlates with their hallucinogenic potencies in humans and their potencies in a drug discrimination paradigm [7]. The effects of DOM on several behaviors are attenuated by pretreatment with the $5\text{-}HT_2$ antagonists pirenperone and ketanserin [8,15]. Studies of regional brain neurochemistry, however, have not demonstrated the presence of $5\text{-}HT_2$ binding sites in the habenular nuclei. DOM does not in the present study show a greater potency when placed in brain areas relatively rich in $5\text{-}HT_2$ receptor, i.e., prefrontal cortex, as opposed to areas relatively poor in $5\text{-}HT_2$ receptors, i.e., dorsal hippocampus (although this latter area did show the highest ED50, Table 4). Further examination of the actions of DOM in relation to 5-HT receptor subtypes, including possible indirect influences, and behavioral effects will be necessary to resolve this issue.

In summary, DOM shows little change in potency following injection into the lateral ventricles, dorsal hippocampus, prefrontal cortex, lateral habenulae, or the dorsal or median raphe nuclei. DOM tends to be most potent following infusion into the median raphe or lateral habenulae. This spec-

trum of activity differs from the sites that are most sensitive to LSD. The low potency and delayed onset of DOM in affecting operant behavior following intracranial infusion also suggests that a singular drug action at any one of these sites is not able to sustain the overall changes in brain processing that relate to the disruption of this behavior, i.e , multiple sites appear to be involved These data add to the evidence that LSD and DOM produce their effects by acting, directly or indirectly, via different brain 5-HT receptors and/or mechanisms. Further examination of additional sites and/or combinations of sites is desirable to allow for definitive conclusions to be drawn on the receptor-types and sites of action of these drugs.

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