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Behavioral Effects of Intracerebroventricular Administration of LSD, DOM, Mescaline or Lisuride[1]

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MOKLER, D. J. AND R. H. RECH. *Behavioral effects of intracerebroventricular administration of LSD, DOM, mescaline or lisuride.* PHARMACOL BIOCHEM BEHAV **21**(2) 281–287, 1984.—The effects on a fixed ratio-40 (FR-40) operant behavior of intracerebroventricular (ICV) administration of the hallucinogens lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (DOM), mescaline or the non-hallucinogenic LSD-analogue lisuride were compared with intraperitoneal (IP) administration. Infusion of LSD (8.5 to 34 μg) into the left lateral ventricle produced a dose-dependent decrease in reinforcers and an increase in 10-sec periods of non-responding (pause intervals). The time-course of LSD showed a shorter latency to onset after ICV than IP administration. The ED50 for doses increasing pause intervals by ICV administration was 15 μg. This disruption was greater than that produced by IP administration of equivalent doses of LSD (IP ED50: 19 μg). DOM (40 to 120 μg) infused into the lateral ventricle also produced a dose-dependent disruption of FR-40 behavior. ICV DOM also showed a rapid onset to peak effects, but a slower offset than LSD, and was 3 times more potent than systemic administration (ED50s: 58 μg ICV vs. 153 μg IP). Mescaline was much more potent in disrupting FR-40 behavior by the ICV route than by IP administration. The ICV ED50 for doses of mescaline increasing pause intervals was 74 μg, in contrast to an ED50 following systemic administration of 2251 μg, demonstrating a 30-fold difference in potency. Lisuride administered *via* the ICV route was no more potent than by IP administration with ED50s of 4 μg ICV and 4 μg IP. Lower doses of lisuride administered by both routes had a similar effect over time on pause intervals. The highest dose produced a peak effect early after ICV administration while IP administration produced a peak effect late in the session. These data suggest differences in the sites of action of these drugs. Alternatively, the differences in the relative efficacies of ICV administration of LSD, DOM, mescaline and lisuride may reflect differences in rates of distribution and/or metabolism of these drugs.

Intracerebroventricular LSD DOM Mescaline Lisuride Operant behavior

THE central site(s) of action of hallucinogenic drugs have not been determined. Behavioral research has indicated that 5-hydroxytryptamine (5-HT) neuronal systems have a primary role in the effects of the hallucinogens [2–4, 7, 10, 11]. The major loci of 5-HT neuronal cell bodies, the raphe nuclei, as well as many nuclei on which 5-HT projections terminate in the forebrain, are periventricular [1,12]. The dorsal raphe nucleus is located on the ventral surface of the cerebral aqueduct, while the median raphe is ventral to the dorsal raphe. The efferent projections of these nuclei to the forebrain terminate in the amygdala, septum, basal ganglia, cortex, hippocampus and ventrolateral geniculate, all of which have some portion in close proximity to the ventricular system. In addition, the habenula forms part of a major route of descending fibers from the forebrain to the midbrain raphe [16]; the habenula is also innervated by the median raphe. Furthermore, this structure is in close apposition to the ventricular space.

Intracranial administration of the 5-HT neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) has furnished evidence that the effects of the hallucinogens on fixed ratio-40 (FR-40) behavior are mediated by central actions [3,4]. Administration of 5,7-DHT into the lateral cerebral ventricle depleted 5-HT in forebrain areas and potentiated the behavioral effects of LSD, DOM and mescaline [3]. When 5,7-DHT was infused into the median forebrain bundle, a major pathway of ascending 5-HT fibers to forebrain areas, the behavioral effects of LSD were potentiated and the effects of DOM attenuated, while the effects of mescaline were unchanged [4]. This suggests that there are differences in the mechanisms and/or sites of action of these hallucinogens.

The local infusion of hallucinogens into the brain gives additional evidence of central sites of action. Minnema *et al.* [6] have shown that rats trained to discriminate LSD from saline generalize the cue from systemically-administered LSD to infusion of LSD into the dorsal raphe nucleus. In

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addition, disruption of an FR-30 operant behavior by intraventricular infusion of mescaline has been reported by Tilson and Sparber [17,18]. Therefore, intracranial administration of hallucinogenic drugs produces effects that mimic to a considerable degree the effects observed following systemic administration.

The purpose of the present experiment was to determine the effects on an operant behavior of infusion into the lateral cerebral ventricle of LSD, DOM, mescaline or lisuride and to compare these effects with those observed after systemic administration of these drugs. These experiments are part of a series of studies to evaluate the effects of these drugs applied locally to brain areas receiving serotonergic input.

METHOD

Subjects

Male Sprague-Dawley rats (Harlan, Indianapolis, IN) were obtained weighing 250–275 g. Animals were housed individually in plastic cages in a temperature-controlled room with a natural light cycle and free access to tap water. The animals were food-deprived to 70–80% of their free-feeding body weights and supplemental food was given following operant sessions to maintain this range of weights.

Training and Operant Procedure

Animals were trained to press a bar for food presentation in a standard operant chamber (LVE). After stable responding was achieved on a continuous reinforcement schedule, the schedule was gradually increased to fixed ratio-40 (FR-40); i.e., 40 presses of the lever were required for presentation of one 45 mg food pellet (Bio-Serv. Inc., Frenchtown, NJ).

Surgical Procedure

After the animals had become trained in the operant schedule, anesthesia was induced with Equithesin (3 ml/kg) and stainless steel guide cannulae were implanted into the left lateral cerebral ventricle. With each rat mounted in a standard Kopf stereotaxic apparatus, 10-mm, 23-gauge lengths of stainless steel tubing were placed so that the tip was located at A: 0.0, L: 1.5, V: 3.3 from bregma [9]. Stainless steel screws were placed into the skull and secured along with the guide cannula with dental acrylic. An 11 mm length of stainless steel wire was placed into the guide cannula at all times except during ICV infusion of drugs.

Retraining and Testing

Following recovery from surgery the rats were again placed into the operant chambers in daily 40-min sessions. Once stable rates of responding on the FR-40 schedule had been re-established subjects were either infused ICV or injected systemically with a drug on Wednesday and Saturday, with intermediate days serving as control days. Infusions were given in random order immediately before the test session; intraperitoneal injections were given in random order but after all intraventricular doses had been administered.

Infusion was performed using a 50 μl Hamilton syringe with PE10 tubing attached to the syringe. The infusion cannula consisted of a length of 30 g stainless steel tubing bent at an obtuse angle 11 mm from the end. Subjects were accommodated to gentle hand restraint during insertion of the infusion cannula. During ICV infusions animals were allowed to roam freely in their home cages. Infusions were accomplished with a Harvard Infusion pump administering a total volume of either 4 or 8 μl over a 55 or 110 sec period, respectively. All systemic injections were IP in a volume of 1 ml.

Two groups of 7 rats each were used to establish the dose-response curves for intraventricular and intraperitoneal administration of LSD or DOM. Three animals were used to determine the effects of mescaline by both routes. Effects of lisuride were examined in 6 animals. Therefore, only one drug, by both routes, was analyzed in each group of subjects.

The number of reinforcers presented and the number of pause intervals produced during the 40-min session were recorded. At the beginning of the session a 10-sec timer was started and each response on the lever before 10 sec had transpired would reset the timer. However, if no response was made for 10 sec the timer reset automatically and a pause interval count was recorded. Reinforcers and pause interval scores during sessions following drug treatments were compared with these values on the control day immediately before.

Following behavioral testing animals were again anesthetized with 3 ml/kg Equithesin. Evans blue dye (4 μl) was infused into the cannula over 1 min. The rats were then perfused with 10% buffered formalin via intracardiac catheter and the brains carefully removed and post-fixed in 10% buffered formalin. Cannula placement was verified by cannula tract and presence of dye. Evidence of pathological changes were noted and correlated with observations during behavioral testing.

Drugs

LSD tartrate, DOM HCl and mescaline HCl were supplied by the National Institute on Drug Abuse (Bethesda, MD). Lisuride hydrogen maleate was the gift of Schering AG (Berlin, FRG). All doses refer to the weight of the salt. The drugs were dissolved in distilled water for IP injection and in a solution of 2.3 mM Ca Cl_2 in 0.9% saline for ICV infusions.

Statistical Analysis

Individual dose-response curves were analyzed using a one-way analysis of variance with least significant difference test for individual comparisons [14]. A two-way analysis of variance was utilized to compare the dose-response curves of ICV LSD, mescaline or lisuride with IP LSD, mescaline or lisuride; the least significant difference test was used for individual comparisons. Since the dose-response curves for ICV and IP DOM did not contain equivalent doses ANOVA analysis was not possible. ED50s for pause intervals were determined by probit analysis.

RESULTS

Rats implanted with intracerebroventricular (ICV) cannulae performed in the FR-40 paradigm at baseline rates of 110 ± 7 reinforcers and 32 ± 3 pause intervals (mean$\pm$S.E.M., $n=22$) during daily 40-min sessions. If fluid was noted at the top of the cannula during drug infusion, the data from that day was not used. Animals were eliminated from the study if histological examination did not verify cannula placement in the lateral ventricle.

Infusion of LSD into the lateral ventricle produced a dose-dependent decrease in reinforcers and reciprocal increase in pause intervals. The time-course of the effect on

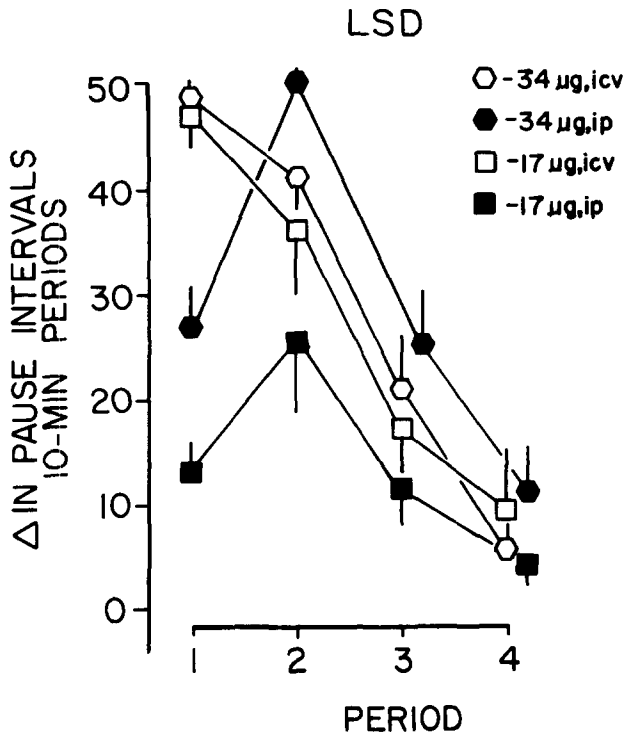

FIG. 1. Time-course of the effect of LSD on pause intervals following ICV (open symbols) or IP (closed symbols) administration. Abscissa represents successive 10-min periods for 40-min FR-40 session. Only the two highest doses of LSD by both routes are shown.

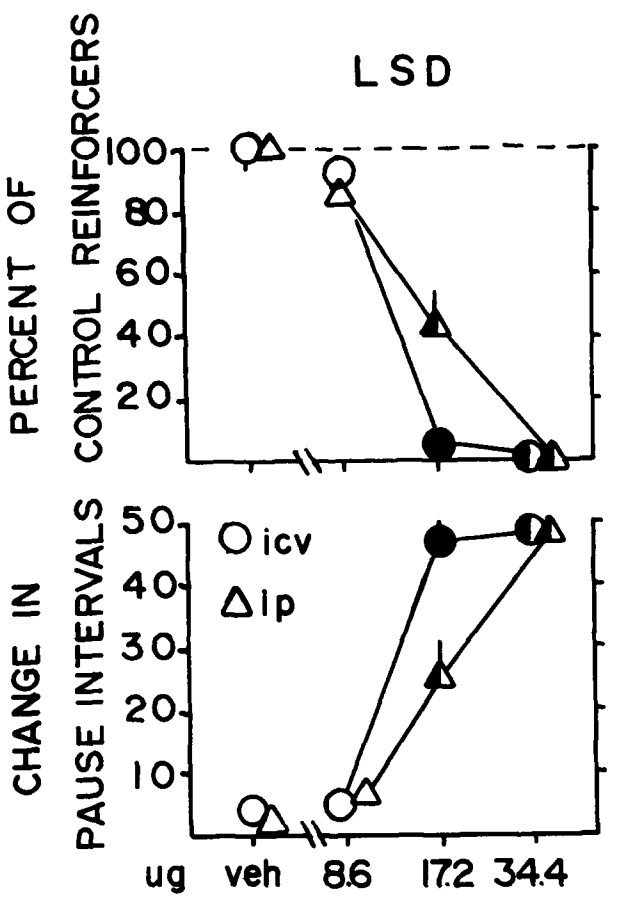

FIG. 2. Peak effects of LSD following ICV (circles) or IP (triangles) administration. Symbols shaded on the left half represent a significant difference from either ICV vehicle or IP saline ($p<0.05$, one-way analysis of variance, least significant differences test), while shading on the right of a symbol represents a significant difference of the effect by the ICV route from that following IP administration ($p<0.05$, two-way analysis of variance, least significant differences test).

pause intervals of ICV and IP administration of LSD is shown in Fig. 1. The peak effect of ICV administration was seen in the first 10-min period of the 40-min operant session, whereas IP administration produced a peak effect during the second period. By both routes of administration the effect of LSD was greatly attenuated by the end of the session. The dose-effect relationship of the effect of LSD to decrease reinforcers and increase pause intervals by ICV and IP routes of administration is shown in Fig. 2. The ICV ED50 for doses that increased pause intervals was 15 µg (Table 1). Intraperitoneal administration of LSD produced a similar disruption with an ED50 of 19 µg. LSD administered IP was significantly less effective in increasing pause intervals than by the ICV route, $F(1,48)=7.152$ for pause intervals, $p<0.01$.

The time course of the effect of DOM on pause intervals is shown in Fig. 3. The peak effect of ICV infusion was seen during the first period, whereas the peak effect for IP injection occurred after the first period. In contrast to the effect of LSD, the effect of DOM on pause intervals was slow in offset, with the effect of the high dose ICV (120 µg) being close to maximal during the last period. This was also true for the IP route, with the low dose (0.5 mg/kg) reaching a peak effect only by the end of the 40-min session. Higher doses of DOM by the IP route (1.0 and 2.0 mg/kg) produced peak effects during the 3rd and 2nd periods, respectively, but maintained prominent effects during the fourth period. DOM by ICV administration produced a disruption of FR-40 behavior that was similar to that after IP administration of the drug (Fig. 4), increasing pause intervals with ED50s of 58 µg and 153 µg after ICV

TABLE 1

ED50s FOR CHANGES IN PAUSE INTERVALS, ICV vs. IP ADMINISTRATION

Drug	ICV (µg)	IP (µg)
LSD	15* (10–19)†	19 (15–24)
DOM	58 (13–83)	153 (45–223)
Mescaline	74 (38–109)	2251 (1560–3142)
LIS	4 (3–6)	4 (2–6)

*ED50s determined by probit analysis using data illustrated in Figs. 1–8.

†Numbers in parenthesis are 95% confidence intervals.

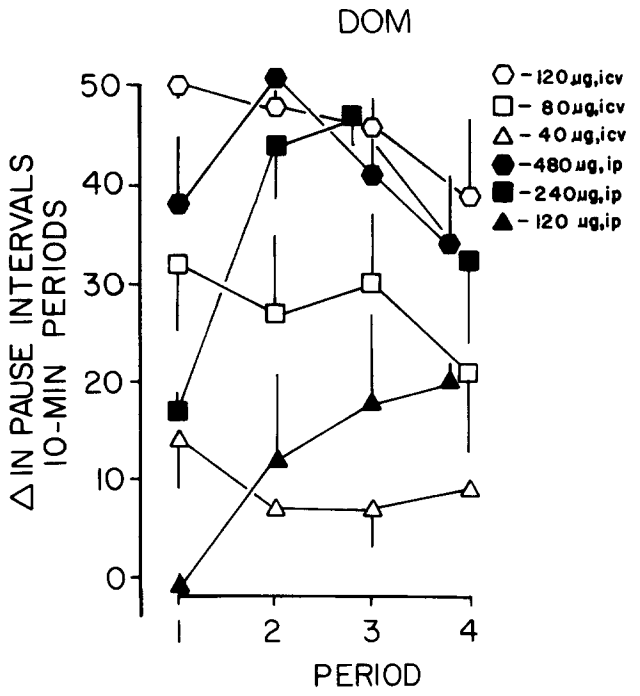

FIG. 3. Time-course of the effect of DOM on pause intervals following ICV (open symbols) or IP (closed symbols) administration.

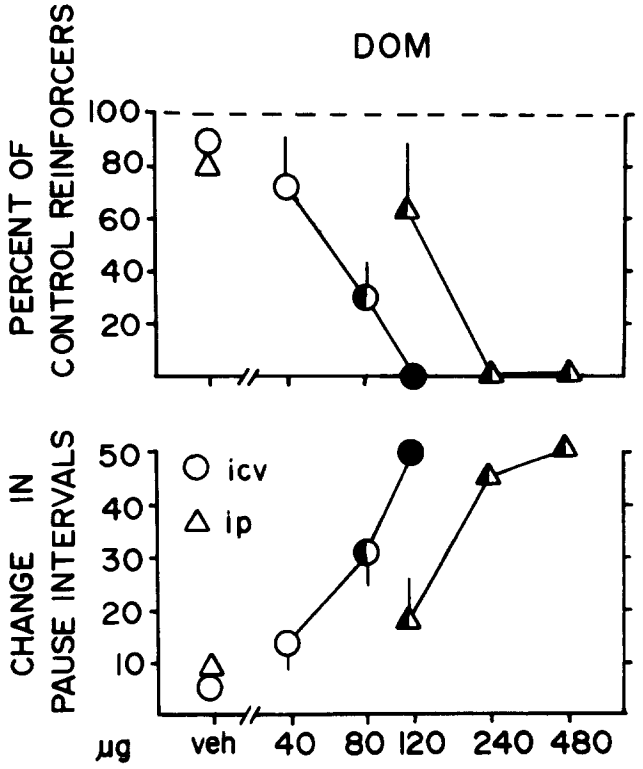

FIG. 4. Peak effects of DOM following ICV (circles) or IP (triangles) administration. Symbols shaded on the left half are significantly different from either ICV vehicle or IP saline ($p<0.05$, one-way analysis of variance, least significant differences test).

and IP administration, respectively (Table 1). This was an approximate 2.7-fold increase in potency for ICV administration compared to IP DOM.

The peak effects of ICV mescaline were observed only in the 4th 10-min period (Fig. 5). In contrast, mescaline administered IP caused an increase in pause intervals which was maximal in the 2nd and 3rd periods. The dose-response curves for ICV and IP mescaline are shown in Fig. 6. Infusion of mescaline into the lateral ventricle was 30 times more potent, with an ED50 of 74 µg for increasing pause intervals in contrast to an ED50 of 2251 µg by the IP route (Table 1).

The time-course for the effects of lisuride on pause intervals is shown in Fig. 7. The lower doses of lisuride follow similar time-courses by both routes of administration with peak effects in the 3rd period, except for the highest dose levels. The highest ICV dose of lisuride had a peak effect during the 1st period, whereas the highest IP dose reached the peak effect during the 4th period of the session. Lisuride also produced a response pattern characteristic hallucinogens when given by either the ICV or IP routes (Fig. 8). The ICV and IP effects for lisuride both occurred with an ED50 of 4 µg (Table 1), so that there was no difference between the two routes of administration, $F(1,35)=0.241$ for pause intervals.

DISCUSSION

Baseline behavior in the FR-40 operant paradigm following cannulation of the left cerebral ventricle in our experimental subjects did not differ from baseline behavior of unoperated animals in other studies [2,7]. Administration of the hallucinogens LSD, DOM and mescaline, and the nonhallucinogen lisuride by ICV infusion produced a disruption

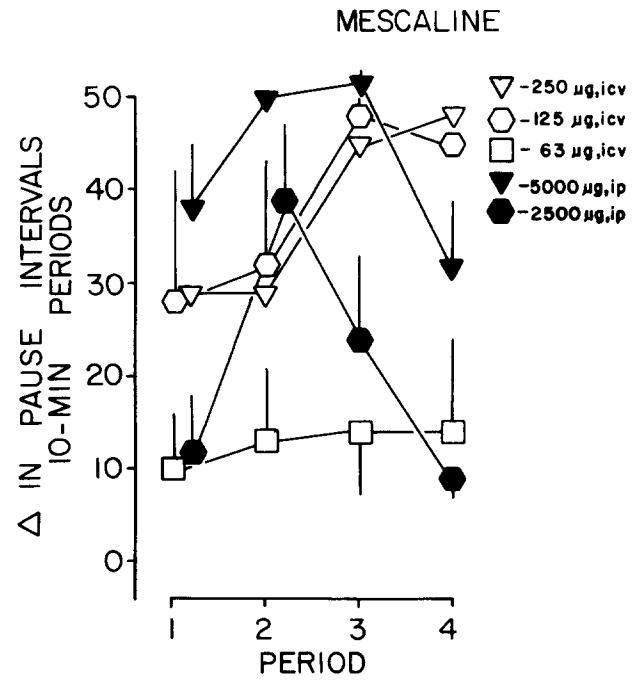

FIG. 5. Time-course of the effect of mescaline on pause intervals following ICV (open symbols) or IP (closed symbols) administration.

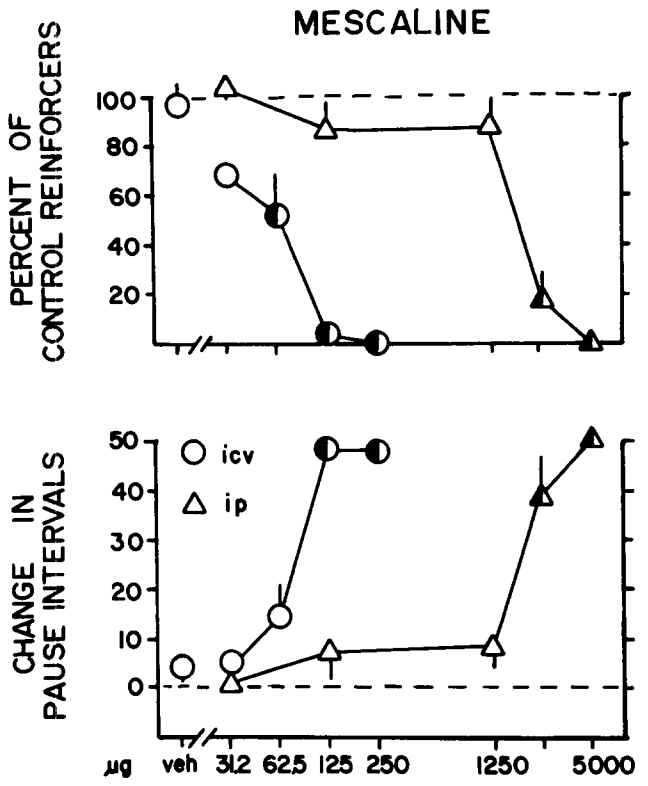

FIG. 6. Peak effects of mescaline following ICV (circles) or IP (triangles) administration. Symbols shaded on the left half are significantly different from either ICV vehicle or IP saline ($p<0.05$, one-way analysis of variance, least significant difference test).

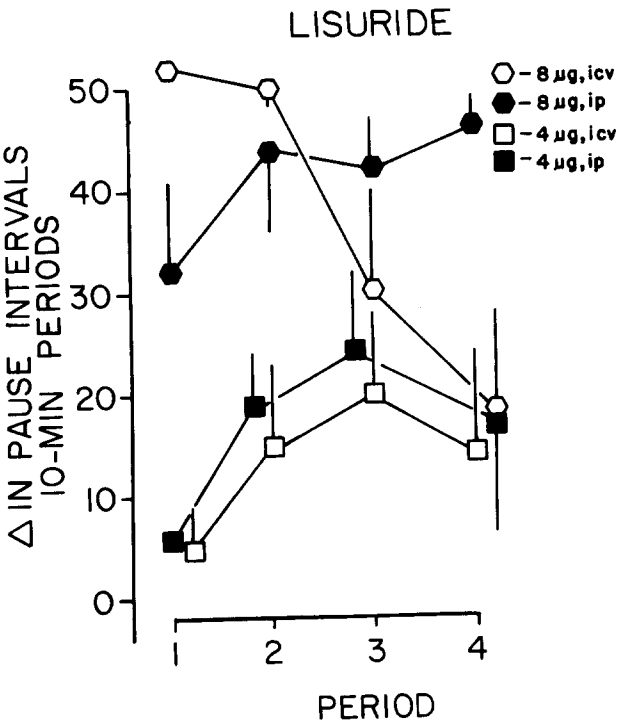

FIG. 7. Time-course of the effect of lisuride on pause intervals following ICV (open symbols) or IP (closed symbols) administration.

of behavior which was similar to that produced by IP administration. This was characterized by a decrease in reinforcers and a reciprocal increase in 10-sec pause intervals. This pattern of disruption has been reported previously following systemic administration of hallucinogenic drugs [2–4, 7, 10]. In addition, other non-hallucinogenic drugs with 5-HT agonistic properties, such as lisuride, quipazine and *m*-chlorophenylpiperazine, also produce a similar disruption of operant behavior [7,10].

Infusion of LSD into the lateral ventricle was approximately 1.3 times more potent than after IP administration. A similar difference in potency was reported by Minnema *et al.* [6] for administration of LSD into the dorsal raphe nucleus of rats trained in a drug discrimination paradigm. The lack of a more potent response to ICV LSD may reflect the ability of systemically administered LSD to reach high concentrations in brain. The time-course of the effect of LSD on pause intervals, however, indicates that differences between ICV and IP administration do exist (Fig. 1). The latency to peak effect following systemic administration agrees with the time to peak brain concentration following injection of 50 μg into the tail vein of mice [15]. Since the shorter latency after ICV administration of LSD suggests a minimal time for distribution to active sites, the small difference in ICV and IP doses may also depend on rapid equilibration at active brain sites by either route. In contrast to these results, the time courses were similar for both the effects of IP administration and

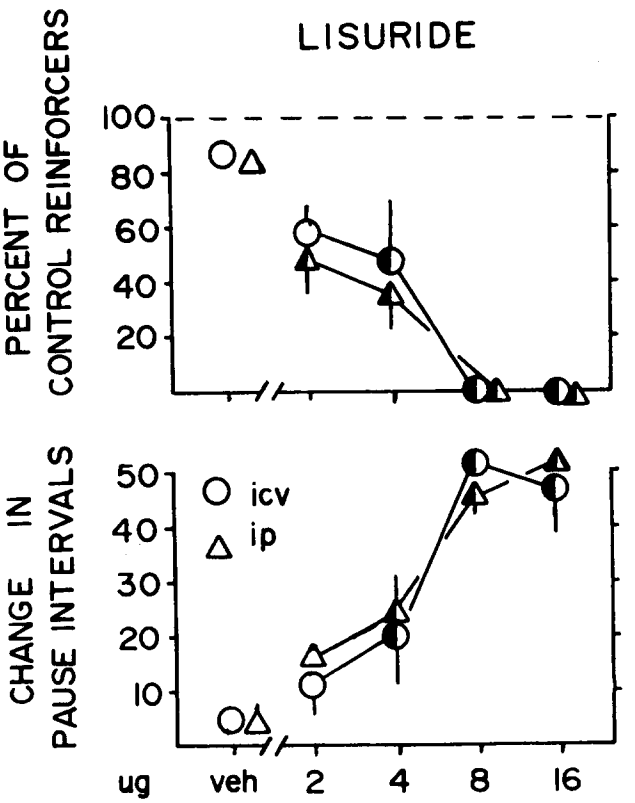

FIG. 8. Peak effects of lisuride following ICV (circles) or IP (triangles) administration. Symbols shaded on the left half are significantly different from either ICV vehicle or IP saline ($p<0.05$, one-way analysis of variance, least significant differences test).

infusion of LSD into the dorsal raphe in rats trained to discriminate LSD from saline [6]. The shorter onset following ICV administration in comparison to infusion into dorsal raphe would suggest that infusion into the lateral ventricle allows more rapid access to active sites. These sites may be one or a number of those forebrain areas receiving 5-HT input (amygdala, septum, hippocampus, cortex, and habenula). The relatively short duration by either route suggests that rapid redistribution and metabolism also make for less differences in potency by the two routes of administration than might have been anticipated. The offset of the effect of LSD by both routes is similar to the reported half-life of LSD in plasma [13].

DOM by ICV infusion was 2.6 times more potent in disrupting behavior than by IP injection. The time-course of this effect indicates that DOM has a much longer duration of action than LSD (Fig. 3). The mean change in pause intervals during the 4th 10-min interval after the highest ICV dose of DOM was 39, even though maximal effects were seen during the first interval. This is in contrast to the time-course of the highest ICV dose of LSD, where the mean change in pause intervals was only 6 during the 4th period. This suggests that both DOM and LSD have periventricular sites of action but that DOM has a longer duration of action due to a slower metabolism and/or diffusion from the brain. This hypothesis receives further support from the time-course of IP injections of DOM, for which DOM has a slow onset that may relate to slow diffusion from the peritoneum. Thus, the greater potency of DOM administered ICV compared to IP may relate to the more limited diffusability of this drug away from its site of infusion or injection.

The infusion of mescaline into the lateral ventricle produced a dramatic effect. In a separate group of cannulated rats (not reported on in Results) a dose of mescaline was given ICV which would have produced a minimal disruption of behavior following IP administration. This dose (1.25 mg) was chosen based on the previous experiments with LSD and DOM which showed approximately equipotent responses with ICV and IP routes. Animals which received this dose showed tonic/clonic convulsions and in 4 out of 5 of these animals death occurred within 3 hours post-infusion.

Infusion of lower doses of mescaline into the cerebral ventricles disrupted operant behavior in a manner similar to higher doses administered IP (Fig. 6). The ED50s for pause intervals indicate a 30-fold greater potency following ICV administration than IP administration. The time-course of the effects of mescaline on pause intervals (Fig. 5) also differs from LSD and DOM time-courses (Figs. 1 and 3, respectively). Whereas the latter produced peak effects in the first 10-min period after ICV administration, mescaline showed peak effects only in the last period. This, along with the differences in potency, suggests that differences in the potency of mescaline and DOM may relate more to diffusion limits than site(s) of action. In fact, mescaline and DOM are almost equipotent following ICV administration although mescaline requires longer to reach sites of action even when infused intraventricularly.

Tilson and Sparber [17,18] have also investigated the effects of ICV administration of mescaline on operant behavior. In an FR-30 paradigm, mescaline disrupted behavior with an "effective central dose" of 100, 150 and 240 μg in rats weighing 325–375 g. This represents an equivalent dose of 300–720 μg/kg to produce an effect which was characterized as similar to an intraperitoneal dose of 10 mg/kg. The "effective central dose" is higher than the ED50 for pause intervals in the present experiment. This may reflect the greater sensitivity of the pause interval measure and the FR-40 schedule to disruption by hallucinogens.

The dose-response pattern of the disruption induced by lisuride following ICV infusion is not significantly different from that following IP injection. Note the identity of the ED50s for these two routes of administration, 4 μg for both ICV and IP administrations (Table 1). The time-course for this effect of lisuride indicates that, except for the highest dose, the peak effect occurs at about the same time for both ICV and IP injection. This suggests that lisuride may diffuse somewhat more slowly than LSD to active brain sites, as well as away from the peritoneum, to produce its effect. The rate of metabolism of lisuride may also be slower, tending to prolong the duration of action by either route.

The similarity in time-course and ED50s for ICV and IP lisuride, whereas LSD and DOM have shorter onsets and greater potency by ICV route, suggests that the brain areas at which lisuride induces a disruption of operant behavior are not in the same proximity as those areas acted on by LSD and DOM. Microinjection of lisuride into the nucleus accumbens produces a stimulation of motor activity similar to the dopamine agonist apomorphine [19], while LSD infused bilaterally into nucleus accumbens decreases motor activity and antagonizes the hypermotility induced by apomorphine [5]. Taken together with the results of the present experiments, these data suggest differences in the site(s) of action of lisuride and LSD. The present experiments do not, however, show that LSD, DOM and mescaline are acting at the same sites. Studies by Commissaris *et al.* [4] have suggested that the sites of action of these hallucinogens may, in fact, differ. Destruction of ascending 5-HT pathways in the medial forebrain bundle by the neurotoxin 5,7-DHT induces differential changes in the response to LSD, DOM or mescaline. Recent work has demonstrated that the effects of LSD may be mediated, in part, by actions in the prefrontal cortex, while the disruption of behavior by DOM may relate more to effects in the lateral habenula (Mokler and Rech, unpublished observations).

Additional evidence of differences between the mechanisms of action of hallucinogens has become available from studies involving 5-HT antagonists [2, 7, 8]. Commissaris *et al.* [2] reported that the phenethylamine hallucinogens are antagonized by metergoline to a greater extent than are the indolealkylamine hallucinogens. A similar difference has been noted in the antagonism of hallucinogenic drugs by the $5HT_2$ antagonist pirenperone [8]. Mokler *et al.* [7] have shown that the hallucinogens LSD and DOM are antagonized to different extents by the 5HT antagonists metergoline, pizotifen and cinanserin. Furthermore, whereas the effects of lisuride were also antagonized by metergoline and pizotifen, the disruption of FR-40 behavior by lisuride was potentiated by cinanserin. Taken together, these data suggest that the hallucinogens LSD, DOM and mescaline as well as lisuride differ in their mechanisms and/or sites of action.

It is concluded that the hallucinogens LSD, DOM and mescaline, and the non-hallucinogen lisuride disrupt FR-40 behavior when administered ICV in a manner qualitatively similar to the effect after IP administration. These drugs vary in relative potency, however. Mescaline demonstrated the greatest relative potency difference with a dose ratio (ED50 IP/ED50 ICV) of 30. DOM showed the next greatest potency difference with a dose ratio of 2.7. LSD demonstrated a dose

ratio of 1.26, and lisuride had a dose ratio of 0.94. Differences in the rates at which the drugs distribute to active sites, are metabolized, or redistribute to other areas away from active sites may account for these differences in dose ratio. The time-course of the effects of these drugs following ICV and IP administration may also reflect such differences. In addition, the different relative potencies shown by LSD, DOM, mescaline and lisuride following ICV infusion and IP injection may relate to differences in the areas of the brain where these agents exert their effects.

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