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Behavioral Sensitivity to LSD: Dependency Upon the Pattern of Central 5HT Depletion[1]

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JOSEPH, J. A. AND J. B. APPEL. *Behavioral sensitivity to LSD: dependency upon the pattern of central 5HT depletion.* PHARMAC. BIOCHEM. BEHAV. 6(5) 499–504, 1977. – Two experiments were carried out using a fixed ratio (FR) schedule of water reinforcement to determine the efficacy of two serotonin (5HT) depleting agents (p-chloroamphetamine, 5, 7-dihydroxytryptamine) in altering sensitivity to a low dose of LSD (0.02 mg/kg). The results showed that while both p-chloroamphetamine (PCA) and 5, 7 dihydroxytryptamine (5, 7 DHT) were efficacious in reducing whole brain 5HT, only 5, 7 DHT altered LSD sensitivity such that a 0.02 mg/kg dose of LSD given 12 days after 5, 7 DHT administration disrupted bar press behavior. This was not observed in animals given PCA within similar parameters. Moreover, 4 animals given PCA that did not show increased sensitivity to LSD, did show behavioral disruption to LSD (0.02 mg/kg) when they were pretreated with p-chlorophenylalanine. Results are discussed on terms of a possible particular pattern of 5HT depletion that must be achieved before sensitivity to LSD is observed.

LSD Sensitivity Fixed ratio p-Chlorophenylalanine 5, 7 Dihydroxytryptamine p-Chloroamphetamine

CONSIDERABLE evidence supports the hypothesis that LSD and related hallucinogens exert their behavioral effects through interactions with central serotonergic (5-HT) neuronal systems [1, 3, 5, 6]. For example, the administration of p-chlorophenylalanine (PCPA), a compound which depletes serotonin by inhibiting the enzyme tryptophan hydroxylase [20], has been found to potentiate the discriminative stimulus properties of LSD [12] and to alter a characteristic hyperactivity syndrome induced by large doses of LSD (2.6–5.2 mg/kg) [21]. In addition, PCPA has been shown to increase sensitivity to the disruptive effects of small doses of LSD (e.g., 0.02 mg/kg) on fixed ratio (FR) responding maintained by either food [5] or water [18] reinforcement. This effect on FR, however, has been shown to be highly dependent upon the level of deprivation under which the animals are maintained. Thus, when water is used as a reinforcer, PCPA-induces hypersensitivity to LSD only when rats are allowed free access to extra water for 5 min each day 12 hr prior to each FR testing session [18].

Even with this stipulation, PCPA induced changes in LSD sensitivity seem to be highly reliable, and it thus appears that the lowering of central serotonin levels potentiates LSD-induced behavioral disruption. Beyond this, however, very little is known about the necessary changes that must occur within the serotonergic system to

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produce these alterations. That is, is it simply the diminution in whole brain 5HT that is important for increasing the efficacy of LSD or must a particular pattern of central indoleaminergic depletion be created in order for the effect to occur? It is known, for example, that lesions of the medial and dorsal raphe nuclei (B7 and B8 cell groups [13]) have effects upon LSD-induced disruption of FR responding which are similar to those seen after PCPA administration [6]. Since these nuclei give rise to many ascending axons which innervate cortical, striatal, and limbic forebrain structures [14] widespread 5HT depletion is produced in these more rostral areas following such ablations that is similar to that seen following PCPA administration. However, it is not known whether altered sensitivity to LSD is a function of 5HT depletion in these particular serotonergic perikarya or in their terminal projections.

The present experiments were undertaken in a first attempt to examine some of these questions by pretreating rats trained on FR tasks with either intraperitoneal injections of p-chloroamphetamine (PCA) or intraventricular injections of 5,7-dihydroxytryptamine (5,7-DHT). Both of these compounds deplete serotonin, inhibit tryptophan hydroxylase, and block the uptake of 5HT into idoleaminergic neurons [7, 22, 27]. However, PCA has a specific neurotoxic action upon the B-9 serotonergic cell group and essentially spares the B-7 and B-8 groups [16] while 5, 7 DHT has neurotoxic actions upon serotonergic neuronal terminals subserved by the B-9, as well as the B-7 and B-8 cell groups [7].

EXPERIMENT 1

Method

Animals. Thirty-two male albino Sprague-Dawley rats obtained from Charles River Laboratories, Wilmington, MA were used. They were housed in individual cages in a room of constant temperature (22°C) and humidity (40–50%) which was maintained on a 12 hr day-night cycle. Each animal was approximately 90 days old and weighed 200–250 g at the beginning of the experiment.

Apparatus. The behavioral studies were carried out in four commercially available experimental chambers (BRS/LCW Model 143–24). Each box contained a single lever or bar located to the right of one of the sides, a dim 28 V house light, and a dipper which delivered 0.05 ml of tap water. A force of 10–15 g was required to activate the lever. Each chamber was housed in a stall that provided sound- and light-attenuation (BRS/LVE Model 132–02). Experimental events were programmed by solid state circuitry located in an adjoining room; bar-pressing responses were recorded on electro-magnetic counters and cumulative recorders.

Behavioral and pharmacological procedures. Upon arrival, each rat was weighed, coded and placed into its home cage. For at least one week, it was allowed free access to both food and water. During the second week, daily weights were recorded and the animals were deprived of water until they reached 80% of their ad lib weight. Preliminary training was then begun.

The animal was placed in a chamber and the reinforcement dipper was activated manually until the animal drank as soon as the dipper was presented; next, a shaping procedure was instituted to condition the bar-press response. In subsequent 40 min sessions, the number of responses required to obtain reinforcement was raised from 1 to 32.

Phase 1

The animals were given no water outside the chamber during training. The design of the experiment is summarized in Table 1. When response rates were relatively stable on the FR 32 schedule (about 1.8 responses/sec), the animals were divided into two groups so that the mean number of responses did not differ by more than 50 bar presses per session (3412 vs 3440 responses/sessions). Each of the animals in one of the groups (N = 16) received 5 min of water 12 hr before each experimental session; the animals in the other group (N = 16) received no extra water. These conditions remained in effect until the end of the experiment. The extra water – no extra water conditions were employed in order to examine the possible changes in PCA potentiation of LSD effects as a function of degree of deprivation. It had been shown previously that this factor is extremely important in mediating LSD disruption when water is used as a reinforcer [18].

Testing continued until the mean number of responses of the group receiving extra water had declined by 22% from 1.8 (to 1.4 responses/sec). The groups were then further subdivided such that 1/2 the animals in a particular group (N = 8) received an intraperitoneal (IP) injection of 20 mg/kg of p-chloroamphetamine (PCA); control animals (N = 8) were given an IP injection of isotonic saline of equivalent volume (approximately 0.3 ml). All animals were given 12.5 mg/kg of chlorpromazine 1/2 hr prior to PCA or vehicle administration to prevent PCA-induced convulsionss.

During the next 11 days, all 32 animals were given IP injections of saline immediately before testing on FR; on the 12th day, they received an IP injection of 0.02 mg/kg of LSD.

Phase 2

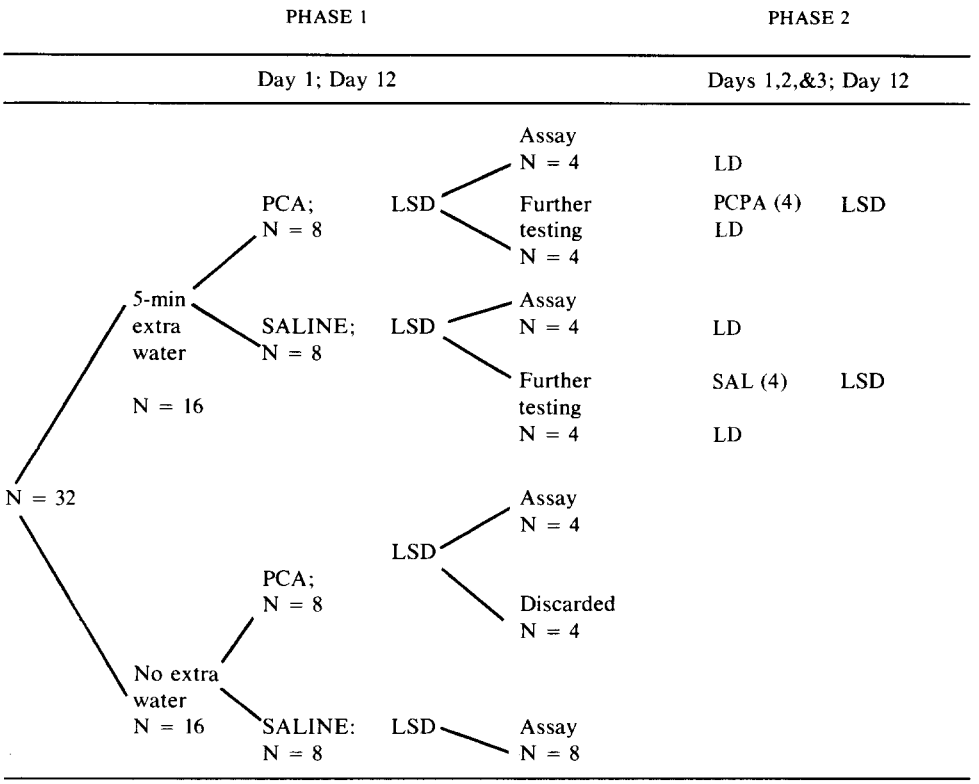
Following the LSD session (Day 12), 20 of the 32 animals were sacrificed by decapitation; central (whole brain) concentrations of 5-HT were determined by a modified column extraction procedure described by Anden and Magnusson [4]. These 20 animals consisted of all of the animals which had been given saline and no extra water (N = 8) plus one half of the animals (randomly selected) in each of the three remaining sub-groups (N = 12).

Of the 12 animals which were not sacrificed, the 4 which had been given PCA and no extra water were discarded. Eight animals which had received extra water and either PCA (N = 4) or vehicle (N = 4) were randomly selected prior to sacrificing the larger group. The animals which had previously been given PCA were given 300 mg/kg of PCPA methyl ester (as free base) in daily doses of 100 mg/kg following testing on FR. The controls (animals previously given saline) received 3 injections of PCPA vehicle (saline) for 3 successive days. All animals were then given saline immediately before FR testing for 11 days after the first PCPA or vehicle injection and continued to receive extra water. On the 12th day, each animal received a second injection of 0.02 mg/kg of LSD immediately before FR testing.

Data analysis. Response rates during LSD sessions were converted to percent control scores by dividing each

TABLE 1

DESIGN OF EXPERIMENT 1



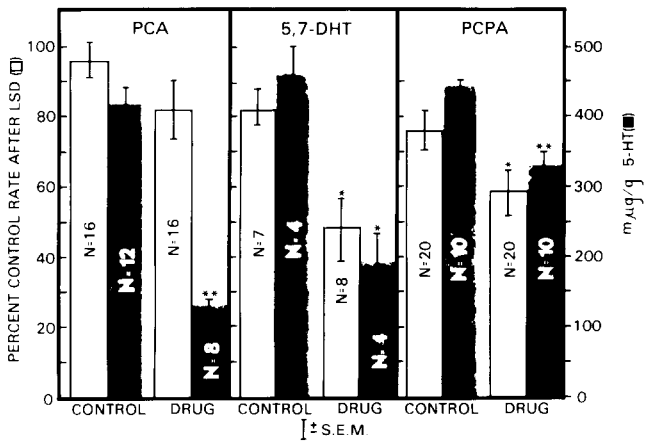


FIG. 1. Shows the percent of control responses (left ordinate, unshaded bars) or m μg whole brain 5-HT (right ordinate, shaded bars) for animals given either PCA (left portion of graph) or 5,7-DHT (middle portion of graph). Right portion of figure depicts similar findings for PCPA from a previous experiment (Joseph and Appel [18]).

animal's response rate following LSD by its rate during the 4 days prior to PCPA or saline administration (base line) and multiplying by $100 \frac{\text{(LSD Response Rate}}{\text{(Base line Response Rate}} \times 100)$.

Difference scores were computed by subtracting the percent of control responses following the second LSD injection (when the animals were pretreated with PCPA or vehicle) from those calculated after the first LSD injection (i.e., when the animals were pretreated with PCA or vehicle).

Results

Not surprisingly, the daily allowance of 5 min of water lowered the overall rate of bar-pressing on the FR 32 schedule of reinforcement (mean rate of extra water group = 79.6, SE = 7; mean rate of no-extra water group = 98.5, SE = 6.7). While these differences were statistically significant, $F(1,28) = 4.0$, $p<0.05$, the extra water had no effect on any of the drug-behavior interaction ($F<1$), and is, therefore, ignored in the presentation which follows. Thus, in Fig. 1, the percent control responses of the PCA and vehicle groups following the administration of LSD (0.02 mg/kg on Day 12) (left portion, unshaded bars) is pooled over extra water and no-extra water conditions. While PCA appeared to lower response rate, there was no significant difference between the groups, $F(1,28) = 2.38$, $p>0.10$. Thus, under the conditions of this experiment, PCA can not be said to alter the amount of behavioral disruption induced by a low dose of LSD (i.e., to alter sensitivity to this compound).

The left portion of Fig. 1 (shaded bars) also shows the effects of PCA (20 mg/kg) on concentration of 5-HT (pooled over extra water and no-extra water conditions). It

is clear that the neurotoxin caused a substantial and significant depletion of 5-HT, $F(1,16) = 22.9$, $p<0.0004$, at about the time behavioral effects of LSD were measured (animals were sacrificed on Day 12). Thus, significantly lowered concentrations of 5-HT in whole brain was not sufficient to cause behavioral disruption following LSD.

There was no differential depletion produced by PCA in the extra water and no-extra water groups ($F<1$).

When PCPA (a drug known to alter sensitivity to LSD[5], was given to animals previously pretreated with PCA, a large LSD-induced decrease in response rate occurred. This is reflected in the mean difference scores (above) which, in PCA-PCPA treated animals was 37.45, and, in controls, was 13.20. Since the differences between these scores was statistically significant, $t(5) = 2.61$, $p<0.05$ (unpooled variances), whereas, no differences in LSD sensitivity had existed previously, $t(4.00) = 1.30$, $p>0.05$, between these groups, it can be concluded that PCPA altered sensitivity to LSD in the same animals in which PCA had no reliable effect.

EXPERIMENT 2

Method

Animals. Twenty-four naive male albino Sprague-Dawley rats obtained from Charles River Laboratories, Wilmington, MA were used in this experiment. They were housed and maintained as in Experiment 1.

Apparatus. The behavioral testing apparatus was the same used as that in Experiment 1. A Kopf stereotaxic apparatus (D. Kopf Instruments, Tujunga, CA) was used for accurate placement of the intraventricular injections and a Hamilton 25 μl syringe was used to deliver the 5, 7 DHT or vehicle solution.

Procedures. Sixteen animals were used in the behavioral experiments. The weighing, coding, and training procedures were the same as those of Experiment 1. Since no differences were seen between the extra water – no-extra water conditions in Experiment 1, it was felt that the parametric manipulation of deprivation was not necessary. Thus, all subjects were given 5 min extra water 12 hr before each FR session in order to maximize LSD effects. Training continued until all animals showed substantial declines in response rate following the extra water administration.

The animals were then divided into two groups which were selected so that the group mean response rates differed by no more than 50 responses per session. One group of animals (N = 8) each received a 200 μg intraventricular injection (free base) of 5,7-DHT in 20 μl of vehicle (4 μl/3 min of saline containing 1 mg/cc of ascorbic acid to prevent autoxidation of the neurotoxin). The control group (N = 8) received the same volume (20 μl) of vehicle solution intraventricularly but no 5,7-DHT. Intraventricular injections were performed stereotaxically under ketamine (25 mg/kg) plus chloropromazine (2.5 mg/kg) anesthesia; the coordinates were 3 mm posterior to bregma, 1 mm lateral to the midline and 4.5 mm dorsal-ventral measured from the dura [26]. All animals (N = 16) were also given IP injections of desmethylimipramine (DMI) (20 mg/kg) 15 min before 5,7-DHT administration to prevent norepinephrine (NE) depletion [11].

The animals were then allowed two days to recover from surgery during which time they were given free access to water and food in their home cages. Water deprivation was reinstituted on the evening of the second day after intraventricular injection and testing on FR began on Day 3 and continued for 9 additional days. On the 10th day (12 days after central 5,7-DHT or vehicle injection) each animal received a 0.02 mg/kg dose of LSD IP immediately before testing on FR. Response rates during the LSD session were calculated as in Experiment 1.

Since these animals were to be used in later experiments, they were not sacrificed for biochemical assays. Instead, a parallel group of 8 animals which had received control injections of 5,7-DHT (N = 4) or its vehicle (N = 4) and were pretreated with DMI were sacrificed for assay on the 12th day after the intraventricular injections and whole brain 5-HT levels were determined as in Experiment 1.

Results

Figure 1 (middle portion) shows the percent control response rates (unshaded bars) for 5,7-DHT-injected animals and vehicle controls following LSD (0.02 mg/kg). As can be seen, the group which received central administration of 5,7-DHT exhibited a considerably lower overall response rate (38.08%) than that of controls. A t-test conducted on the data using unpooled group variances showed that this difference was significant, $t(9.23) = 2.79$, $p<0.05$. Thus, disruptive effects of LSD on behavior were potentiated by 5,7-DHT.

Figure 1 (middle portion) also shows that 5,7-DHT lowered whole brain concentration of 5-HT (shaded bars). This difference in biogenic amines was both large (60%) and statistically significant, $t(6) = 5.84$, $p<0.01$). It should be pointed out that while these assay data are from nonbehaving animals the 60% depletion produced by intraventricular 5,7-DHT administration (200 μg) has been a constant finding in both nonbehaving and behaving animals in our laboratory. Hence neither LSD administration nor behavioral testing seems to alter the effects of 5,7-DHT on amine concentration. It should also be noted here that DMI effectively prevents depletion of NE following 5,7-DHT (not shown in Fig. 1); the concentration of NE in 5,7-DHT treated animals is comparable to those of nontreated animals previously assayed in our laboratory (i.e., 0.303 ug/g) (see also Bjorklund, Baumgarten and Rensch [11]).

DISCUSSION

The results of these experiments can be summarized as follows: (a) PCA did not alter sensitivity to LSD (0.02 mg/kg) even though the PCA injected animals showed a substantial depletion in whole brain 5HT (approximately 76%) and 1/2 the PCA-injected animals had received extra water (b) in animals in which PCA did not previously potentiate the disruptive effects of LSD on FR, PCPA did not potentiate these effects (c) central administration of 200 μg of 5,7-DHT (and extra water) altered sensitivity to LSD in much the same manner as raphe lesions and PCPA administration [5,6].

Thus, there seems to be a differential effect of PCA and 5,7-DHT on LSD-induced changes of FR performance. The precise nature of this difference requires further delineation, but it does not seem to be due to disparities in the efficacies of these drugs to reduce whole brain 5-HT concentrations. Substantial reductions in this monoamine were noted following both PCA and 5,7-DHT. In fact, PCA produced greater reductions in central 5-HT levels than did PCPA, 5,7-DHT (Fig. 1), or raphe lesions [6]. This finding with regard to PCPA is illustrated in Fig. 1 (right portion)

where it can be seen that PCPA (300 mg/kg) only produced a 26% decrease in central 5-HT that was concomitant with LSD-induced behavioral disruption when measured 12 days after the last PCPA injection (from Joseph and Appel [18]). Because 5,7-DHT has been shown to deplete central catechol – as well as indole – amine containing fibers [7], and catecholaminergic involvement has recently been implicated in the behavioral actions of high doses of LSE [19], it might be expected that this factor could account for the differences between the PCA and 5,7-DHT. This contention is supported by the finding that both PCPA and 5,7-DHT deplete central NE as well as 5 HT [7, 20, 23] and also by the present results in which PCPA effectively altered sensitivity to LSD in animals previously given PCA. However, DMI was given to the 5,7-DHT-injected animals prior to surgery to increase its specificity [11] and the effects of PCPA on adrenegic neurons has been shown to be minimal at the time of LSD administration, i.e., 12 days after the last PCPA injection [24]. Additionally, neither 5,7-DHT nor PCPA have been reported to alter central dopamine (DA) levels [7,20]. Moreover, pretreatment with alpha methyl tyrosine which of course depletes both DA and NE inhibiting tyrosine hydroxylase does not potentiate the effects of LSD, while raphe lesions do potentiate these effects [5,6]. Thus, possible influences of 5,7-DHT or PCPA on catecholaminergic systems cannot explain our results. Rather, what is suggested here and elsewhere [8] is that the effects of LSD are somehow dependent upon the integrity of the 5-HT neuronal system. Obviously, a very small alteration in 5-HT concentration is necessary to observe a change in sensitivity to LSD, especially when the animals are given 5 min of extra water 12 hr prior to FR behavioral testing. Since PCA and 5,7-DHT have different effects on both sensitivity to LSD and patterns of 5-HT depletion within the central serotonergic system, it would appear that this pattern of central depletion is important in determining LSD effects on FR behavior.

The drug and surgical regimens described above (e.g., PCPA, 5,7-DHT) are effective in depleting 5-HT when this amine is measured 12 days after treatment [5, 7, 15, 27]. However, the pattern of depletion following PCA differs from the other treatments in at least one important respect. Very little 5-HT depletion or alteration in tryptophan hydroxylase activity has been noted in the midbrain raphe nuclei (B7 and B8) groups following PCA [10, 16, 25]. Conversely, 5,7-DHT, PCPA and raphe lesions produce substantial amounts of depletion in these cell groups [6,7]. These nuclei (B7 and B8) have been shown to be intimately involved in mediating certain behavioral effects of LSD [2,17]. It is possible that altered activity of 5-HT in neurons which have their cell bodies in these nuclei (or in postsynaptic neurons which are innervated by B7 and B8 neurons) is a necessary condition for the altered sensitivity to LSD to be seen. It is known that the stereospecific binding of [H3] LSD to various rat brain regions may involve presynaptic storage elements [8,9]. Moreover, LSD does not bind equally to all brain areas. The highest concentrations are usually found in the cerebral cortex and limbic areas, which receive the majority of their serotonergic input from the B7 and B8 groups – groups which are essentially spared by PCA. If these areas are not differentially effected by PCA in a manner other than a lowering of tryptophan hydroxylase or regional 5-HT levels, then the LSD-behavioral interactions at the dose levels employed here may not be found. It might also be mentioned here that more recent findings [23] have shown that the terminal projections of the B8 cell groups are more severely affected by PCA than those of the B-9, again pointing out the importance of possible changes in the nuclei themselves in mediating the effects of LSD.

The finding that PCA-injected subjects later given PCPA showed altered LSD sensitivity provides some support for this suggestion. However, further research is necessary to determine (a) if these PCA-5,7-DHT relationships hold with regard to other hallucinogens and (b) whether PCA or 5,7-DHT administration will alter LSD binding in various central and limbic areas. Nevertheless, the data do provide strong evidence that the 5-HT neuronal system, especially the B7 and B8 cell groups may be somehow important in altering behavioral sensitivity to LSD.

ADDENDUM

It must also be noted here that following the completion of this study, the 5,7-DHT-injected animals and their controls were further tested with the FR paradigm following either mescaline, psilocybin, phencyclidine, quipazin or amphetamine administration. The behavioral data from these tests will be reported elsewhere. However, biochemical analyses of the whole brain levels of 5-HT and NE showed that 5-HT was depleted by 57% to 0.160 ± 0.072 μg/g. Control (vehicle injected) animals showed a mean of 0.369 ± 0.042 μg/g of serotonin ($t(12) = 6.32$, $p<0.01$). Norepinephrine levels, however, were similar in both 5,7-DHT injected animals and their controls (0.349 ± 0.067 μg/g, 0.360 ± 0.18 μg/g respectively; $t(11) = 0.18$, ns.). Thus, both the efficacy and specificity of 5,7-DHT when used in conjunction with DMI was confirmed at 45 days after the 5,7-DHT administration in these behaving animals.

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