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Phencyclidine, Lysergic Acid Diethylamide, and Mescaline: Cerebral Artery Spasms and Hallucinogenic Activity

Abstract. *Phencyclidine (PCP), lysergic acid diethylamide (LSD), and mescaline produced potent contractile responses on isolated basilar and middle cerebral arteries, where, in terms of potency, LSD > mescaline > PCP. All three drugs produced cerebrovasospasm in a concentration range which parallels that needed for their psychotomimetic and intoxicating actions. Specific receptors for PCP, which subserve contraction and differ from those for LSD and mescaline, are found in cerebral arteries. Concentrations of PCP that produced near-maximum contractile responses on cerebral arteries were similar to those in the blood and brain of human subjects who had died from PCP overdoses. A specific calcium antagonist, verapamil, readily prevented (and reversed) PCP-induced vasospasm. This study provides direct evidence for PCP receptors in cerebral blood vessels, the biologic action of which can be reversed by a calcium antagonist; the clinical use of the latter could prove invaluable in treating PCP-intoxicated victims.*

Phencyclidine hydrochloride intoxication, especially among young people, is reaching alarming and epidemic proportions (*1, 2*). Abuse of phencyclidine hydrochloride, often referred to as "PCP," "angel dust," or "hog," frequently appears to result in violent behavior and mortality among its users. Systemic administration of PCP, like lysergic acid diethylamide (LSD) and mescaline, has a profound effect on mental status, causing, for example, disorientation, psychosis, uncontrolled violent reactions, and convulsions; some individuals may experience hallucinations and a condition that has been linked to schizophrenia (*1, 2*). High doses of these drugs often lead to severe hypertension, a toxic acute brain syndrome (manifested by disorientation), a clouding of consciousness, and convulsions (*3, 4*). Mortality following ingestion of PCP, LSD, or mescaline is thought to be a result of cardiovascular or respiratory failure, the mechanisms of which are not clear (*3, 4*).

Since cerebral hypoxia has been suggested as playing a role in the psychotomimetic and lethal actions of PCP, LSD, and mescaline (*1–5*), we wondered whether these hallucinogenic drugs could exert direct actions on cerebral blood vessels. We report here that PCP, LSD, and mescaline produce vasospasm of isolated cerebral arteries; the ranges of the effective contractile concentrations parallel the psychotomimetic, intoxicating, and lethal concentrations of all three hallucinogenic drugs. The cerebral contractile effects of PCP could be completely abrogated (or prevented) by use of a calcium antagonist (verapamil) but not by any known specific pharmacologic antagonist.

Mongrel dogs of either sex weighing 15 to 20 kg were anesthetized with pentobarbital sodium (30 mg/kg). After thoracotomy, the brains were rapidly removed and the basilar and middle cerebral arteries were excised. Helical strips were cut from segments of these cerebral arteries; the strips were 10 to 15 mm long by 1.5 to 2.0 mm wide (*6*). The strips were suspended isometrically under 1 g of tension and incubated in 20-ml muscle chambers containing normal Krebs-Ringer bicarbonate solution (composition in millimoles per liter: NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $MgSO_4$, 1.2; glucose, 10; and $NaHCO_3$, 25) at 37°C, through which a mixture of O_2 (95 percent) and CO_2 (5 percent) was bubbled (*6*). The force of the contractions was measured with Grass FT-03 force-displacement transducers and recorded on a Grass model 7 polygraph. Three hours after being incubated under tension, the preparations were exposed to KCl, serotonin (5HT), PCP, LSD, and mescaline. The KCl and 5HT were used as stimulants so that we could assess the vasoactive effects of the psychotomimetic drugs.

Addition of LSD or mescaline to the muscle chambers resulted in rapid, increased tension development in all cerebral arteries tested. This effect was followed shortly by a falloff in tension to a lower plateau, very similar to that observed for 5HT and KCl (Fig. 1). Addition of PCP resulted in rapid, increased tension development which was long-lasting and did not decrease in magnitude with time (Fig. 1). Cumulative addition of the psychotomimetic drugs to the cerebral vessels revealed that a relative order of contractile potency (based on threshold and half-maximum concentrations) can be obtained, where LSD > mescaline > PCP (Table 1 and Fig. 2). A comparison of these contractile concentrations to those needed for psychotomimetic and intoxicating actions in man not only reveals a parallelism (*1–4, 7*), but also demonstrates that the relative order of potencies, that is, LSD > mescaline > PCP, are also similar. Possibly more important was the finding that the concentrations of PCP that yielded near-maximum contractions on the canine middle cerebral and basilar

Table 1. Relative contractile sensitivity of canine basilar and middle cerebral arteries to PCP, LSD, mescaline, 5HT, and KCl. The values are given as means ± standard errors of the means. Minimum effective concentration is the concentration which produces a threshold contractile response. The EC_{50} is the concentration that produces 50 percent of the maximum contractile response.

Drug agonist	N	Minimum effective concentration (M)	EC_{50} (M)	Maximum tension (mg)
		Middle cerebral arteries		
LSD	6	$1.62 \pm 0.35 \times 10^{-9}$	$2.35 \pm 0.38 \times 10^{-8}$	466 ± 65.6
Mescaline	4	$5.15 \pm 1.22 \times 10^{-7}$	$3.75 \pm 0.65 \times 10^{-6}$	516 ± 78.4
PCP	9	$1.58 \pm 0.46 \times 10^{-7}$	$3.42 \pm 0.28 \times 10^{-5}$	676 ± 51.5
5HT	7	$4.97 \pm 0.52 \times 10^{-10}$	$1.42 \pm 0.16 \times 10^{-8}$	520 ± 73.8
KCl	4	$2.24 \pm 0.24 \times 10^{-3}$	$1.24 \pm 0.16 \times 10^{-2}$	700 ± 35.4
		Basilar cerebral arteries		
LSD	6	$2.56 \pm 0.68 \times 10^{-9}$	$2.92 \pm 0.46 \times 10^{-8}$	488 ± 58.4
Mescaline	6	$1.76 \pm 0.36 \times 10^{-7}$	$6.60 \pm 0.82 \times 10^{-6}$	720 ± 52.5
PCP	9	$1.84 \pm 0.52 \times 10^{-7}$	$4.62 \pm 0.44 \times 10^{-5}$	1400 ± 102
5HT	7	$1.97 \pm 0.84 \times 10^{-9}$	$5.88 \pm 0.76 \times 10^{-8}$	1293 ± 184
KCl	4	$4.20 \pm 0.65 \times 10^{-3}$	$1.68 \pm 0.32 \times 10^{-2}$	1325 ± 35.3

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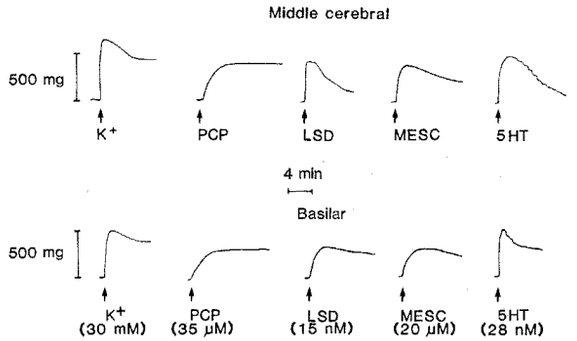

Fig. 1. Responses of canine middle cerebral and basilar arteries to addition of KCl (K^+), PCP, LSD, mescaline (*MESC*), and serotonin (*5HT*). Numbers in parentheses indicate the final concentration of each stimulant in the bath.

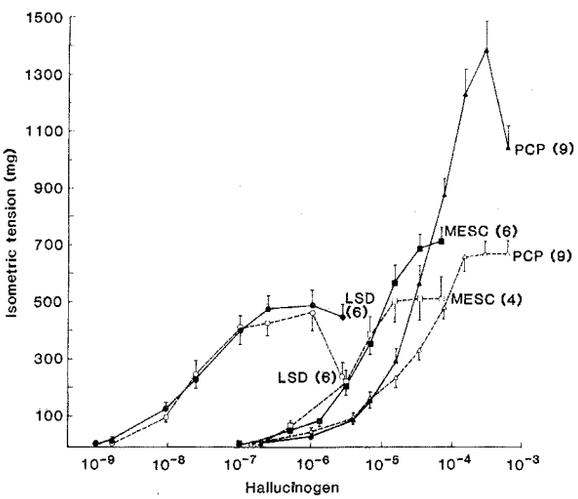

Fig. 2. Comparative contractile potencies of the hallucinogens LSD, mescaline (*MESC*), and PCP. The hallucinogens were tested on isolated canine basilar (closed symbols) and middle cerebral (open symbols) arteries. Figures in parentheses indicate the number of animals used. Each point represents the mean value ± the standard error of the mean (vertical bars).

arteries (that is, 2 to 10 mg/liter) were identical to those in the blood and brains of humans who had died after ingestion of lethal doses of PCP (*8*).

Although we found that maximum contractile effects of both LSD and mescaline could be completely prevented (or abrogated) by a pharmacologic antagonist known to act on 5HT receptors (that is, methysergide, 0.5 μg/ml; $N = 6$ experiments), spasms induced by PCP could not be prevented or reversed by either antiserotonin ($N = 5$), anticholinergic (atropine sulfate, 0.5 μg/ml; $N = 5$), antiadrenergic (phentolamine, 0.5 μg/ml; $N = 5$), or antihistaminic (diphenhydramine hydrochloride, 0.5 μg/ml; $N = 5$) drugs. In addition, indomethacin (1 to 2 μg/ml), when used in concentrations known to inhibit formations of prostaglandins, prostacyclin, endoperoxides, and thromboxanes, did not alter cerebral contractions produced by PCP ($N = 4$). Collectively, such findings suggest that although both LSD and mescaline probably induce cerebral vasospasms via actions on 5HT receptors, PCP elicits cerebral vasospasm by some direct mechanism on cerebral blood vessels, not via actions on 5HT receptors. Such findings tend to support the idea suggested by others that, for some unknown reason, there are specific receptors and binding sites for PCP in the brain (*9*). Our findings suggest that such specific and biologically active PCP receptors might also be located on cerebral blood vessels.

One of the main clinical signs of PCP intoxication (and also of LSD and mescaline intoxication) is an increase in blood pressure (*3, 4*). Since our results suggest that this increase might be due to the direct action of the psychotomimetic drugs on arteries and arterioles rather than by a sympathomimetic action (*10*), we attempted to reverse the contractile actions of PCP. A variety of specific antagonists did not modify the PCP responses; we therefore thought that a calcium antagonist might be effective because all contractile events in muscle tissue are mediated by an increase in the cytoplasmic level of calcium ions (Ca^{2+}). Addition of low concentrations of the calcium antagonist verapamil (1 μ*M*) completely prevented, or reversed, the near-maximum contractile actions of PCP on all cerebral arteries tested ($N = 5$) (Fig. 3). This Ca^{2+} antagonist was also able to prevent (or reverse) the contractile actions of LSD and mescaline on cerebral arteries (Fig. 3). If these findings obtain on human cerebral arteries, Ca^{2+} antagonists might be useful in the treatment of PCP, LSD, and mescaline intoxication, particularly in ameliorating the high incidence of intracerebral hemorrhages and hypertensive encephalopathies associated with PCP abuse (*3*). At present, there is no known agent that effectively antagonizes the biologic actions of PCP (*2*).

It is tempting to speculate that the results reported herein might be important in both the psychotomimetic and lethal actions of PCP. If PCP exerts similar contractile actions on intact brain arteries, such vasospasm could result in cerebral hypoxia, ischemia, and the altered cerebral glucose metabolism recently reported in animals treated with PCP (*5*).

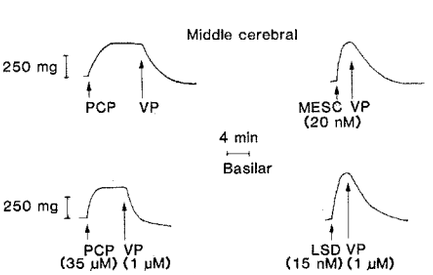

Fig. 3. Addition of verapamil (*VP*) (1 μ*M*) rapidly relaxes cerebral arterial spasms induced by the hallucinogens PCP, mescaline, and LSD.

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