

## The Effect of Acute Phencyclidine Administration on Cyclopropane Requirement (MAC) in Rats

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The effect of acute administration of phencyclidine (PCP) on the anesthetic requirement (MAC) was studied in rats. Rats were anesthetized with cyclopropane and MAC determinations were made by the tail-clamp technique. PCP, 2 or 4 mg/kg, subcutaneously, produced a 32 and 42 per cent decrease, respectively, in cyclopropane MAC. The PCP-induced decrease in MAC was not altered by naloxone treatment indicating that an interaction of PCP with opiate mechanisms is unlikely. Central monoamine depletion with reserpine decreased cyclopropane MAC by 20 per cent. In these monoamine-depleted rats, 4 mg/kg PCP produced a further reduction in MAC of 22 per cent. In rats almost totally depleted of catecholamines by pretreatment with reserpine and  $\alpha$ -methyl-p-tyrosine, a marked (43 per cent) decrease in MAC was observed. The administration of 2 mg/kg PCP, in these catecholamine-depleted rats produced an additional 10 per cent decrease in MAC for a total reduction in MAC of 53 per cent. The effect of PCP in the monoamine- and catecholamine-depleted rats indicates that while an effect on central monoamines may play a part in the mechanism of action of PCP, it is not the sole mode of action of the drug. In patients intoxicated with PCP there is a significant potential for anesthetic overdose as their anesthetic requirement may be much less than would be expected in the nonintoxicated state. (Key words: Anesthetics, gases: cyclopropane. Antagonists, narcotic; naloxone. Brain: catecholamines. Potency, anesthetic: MAC. Toxicity: phencyclidine.)

PHENCYCLIDINE (PCP, "angel dust"), one of the most popular street drugs in this country, reportedly interacts with several types of neurotransmission in the central nervous system. PCP has been variously reported as an amphetamine-like compound,<sup>1-3</sup> an antagonist at dopaminergic autoreceptors,<sup>4</sup> and an opiate agonist.<sup>5</sup> More recent evidence suggests that PCP may act presynaptically on noradrenergic terminals.<sup>6,7</sup> The evidence for an opiate-agonist-like action of PCP is based on a high correlation of activities of PCP and its analogs in the *in vitro* opiate receptor binding assay with *in vivo* behavioral tests.<sup>5,8</sup> Since opiate receptor agonists such as nar-

cotics,<sup>8</sup> amphetamines,<sup>9</sup> and drugs which affect central catecholamine release<sup>10</sup> alter anesthetic requirement (MAC), the effect of acute administration of PCP on cyclopropane MAC was studied in rats.

### Materials and Methods

The anesthetic requirement (MAC) for cyclopropane was determined in forty male Sprague-Dawley rats (250-350 g) using a tail-clamp technique.<sup>11-13</sup> MAC was the anesthetic concentration midway between that permitting and that preventing movement in response to a clamp applied to the middle third of the tail for one minute. Cyclopropane was chosen as the primary anesthetic since, after a short equilibrium time, alveolar and inspired concentrations are essentially equal and the latter concentration can be determined directly from calibrated flow meters. All experiments were performed during daylight hours. The animals' rectal temperature was maintained by a warming mattress between 36°C-37.2°C.

In 17 rats (Group 1) after an initial MAC determination, the femoral artery was cannulated and MAC redetermined. The average of the two MACs was established as the control MAC. Following the second MAC determination, either 2 or 4 mg/kg PCP<sup>¶</sup> were administered randomly subcutaneously (sc) in blinded fashion. MAC was determined beginning 30 min after the administration of PCP, and the per cent change calculated with each animal serving as its own control. Arterial blood gases were determined at MAC levels before and after the administration of PCP.

In eight other rats (Group 2), after the control MAC measurement, femoral arterial and venous cannulations were done. A bolus of naloxone (10 mg/kg) was followed by a continuous intravenous infusion of the drug (0.1 mg · kg<sup>-1</sup> · min<sup>-1</sup> and MAC was determined. Thereafter, PCP (4 mg/kg) was administered sc and MAC redetermined 30 min later. Arterial blood gases were examined during naloxone infusion before and after PCP administration.

In Group 3 (N = 6), the effects of PCP on MAC was

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with relative potencies determined *in vivo* in mouse and rat. Research Communication in Substance Abuse. 1:83-96, 1980.

¶ The drugs used were obtained as follows: PCP (NIDA, courtesy Dr. P. G. Guyenet), naloxone (Endo Lab), reserpine (Ciba-Geigy), DL  $\alpha$ -methyltyrosine methylester HCl (Aldrich).

TABLE 1. Effect of PCP on Cyclopropane MAC

	N	MAC Per Cent Cyclopropane	Per Cent Change in MAC*	Mean PaCO <sub>2</sub> (mmHg)
Control (Group 1)	17	17.7 ± 0.06	—	38.1
PCP, 2 mg/kg	8	12.0 ± 0.33†	32.2 ± 1.4†	39.9
PCP, 4 mg/kg	9	10.2 ± 0.60†	42.1 ± 2.7†	44.1
Control (Group 2)	8	18.4 ± 0.13	—	—
Naloxone	8	18.5 ± 0.20	0.7 ± 1.2†	38.2
Naloxone + PCP, 4 mg/kg	8	11.0 ± 0.20†	40.1 ± 1.3†	42.2
Control (Group 3)	6	17.8 ± 0.17	—	—
Reserpine	6	14.2 ± 0.33†	20.2 ± 1.6†	35.3
Reserpine + PCP, 4 mg/kg	6	10.3 ± 0.31†	42.2 ± 2.1†	42.5
Control (Group 4)	9	16.9 ± 0.31	—	—
Reserpine + AMPT	9	9.7 ± 0.47†	43.4 ± 2.7†	25.4
Reserpine + AMPT, + PCP, 2 mg/kg	9	7.9 ± 0.44†	53.0 ± 2.4†	27.6

† = increase; ↓ = decrease.

All values are means ± SEM.

\* The per cent changes in MAC were calculated from the per cent

changes in individual animals with each animal serving as its own control.

†  $P < 0.05$ .

studied in rats depleted of monoamines by reserpine treatment. Rats were pretreated with 1 mg/kg reserpine intraperitoneally (ip) per day for 2–3 days. MAC determinations were made 24 h after the last reserpine treatment before and after the administration of PCP (4 mg/kg) sc. To achieve a high degree of catecholamine depletion, nine rats (Group 4) were treated with reserpine and the methyl ester hydrochloride of  $\alpha$ -methyl-tyrosine (AMPT), a catecholamine synthesis inhibitor. The regimen suggested by Haeusler<sup>14</sup> was employed which consisted of an initial ip injection of reserpine (5 mg/kg) and AMPT (300 mg/kg, ip) followed 15 hs later by a second injection of AMPT (300 mg/kg, ip). Control MAC was established in each rat prior to the catecholamine depletion. MAC values were studied two hours after the second AMPT treatment, before and after the administration of PCP (2 mg/kg). Statistical analysis was carried out using analysis of variance and  $P < 0.05$  was considered as significant. Comparisons between the different groups were done by the revised least significant difference methods.<sup>15</sup>

#### CATECHOLAMINE ASSAYS

In two control rats and in four animals treated with reserpine and AMPT, assays of norepinephrine content were done in the hypothalamus, the area in the central nervous system with the highest concentration of norepinephrine. After the MAC studies were performed, the animals were killed with 1 ml intravenous saturated KCl. The brain was removed rapidly and placed on an ice-cooled glass plate. Specimens of the hypothalamus were obtained according to the dissecting procedure described by Glowinski and Iversen.<sup>16</sup> The specimens were weighed,

homogenized in 2 ml 0.05 M perchloric acid, centrifuged, and decanted. Samples were absorbed into alumina, washed, and extracted into perchloric acid for assay by high performance liquid chromatography with electrochemical detection using the method described by Felice *et al.*<sup>17</sup> Dihydrobenzylamine was added to the brain specimens as an internal standard. The system was calibrated by the addition of known amounts of norepinephrine to the control brain specimens. The results are expressed as nanograms of norepinephrine per gram of brain tissue.

#### Results

The effect of PCP on the cyclopropane MAC in the four groups is shown in table 1. Control values of cyclopropane MAC in the different groups are comparable to those previously reported in rats.<sup>12,18,19</sup> The decreases in MAC following 2 and 4 mg/kg PCP, were 32 and 42 per cent, respectively. The observed change in MAC following the two PCP doses were significantly different both from the control and from each other ( $P < 0.05$ ).

The inspired cyclopropane concentration had to be decreased by 10 to 15 per cent within 3 to 5 min following the administration of PCP to avoid severe respiratory depression. In the first three rats studied, the inhaled cyclopropane concentration was not altered soon after PCP administration. All three rats died of respiratory depression within five minutes. A transient hypertension (15–18 per cent increase in mean arterial pressure lasting for 6 to 10 min) was also observed following the administration of PCP.

In animals given naloxone, the drug alone had no effect on the MAC of cyclopropane. The decrease in MAC following 4 mg/kg PCP, sc was also not altered

by naloxone treatment. Central monoamine depletion with reserpine (Group 3), resulted in a 20 per cent MAC reduction. The addition of PCP (4 mg/kg, sc) produced a further reduction in MAC by 22 per cent resulting in a total decrease of 42 per cent of control MAC. The additional decrease in MAC following PCP in this group, calculated as a per cent of the post-reserpine MAC, was 25 per cent. Following a high degree of catecholamine depletion (Group 4), there was a marked decrease (43 per cent) in the cyclopropane MAC. The administration of 2 mg/kg PCP, sc. in these catecholamine-depleted rats produced a further decrease in MAC of 10 per cent of control (total reduction in MAC of 53 per cent of control). The decrease in MAC post-PCP administration in these rats expressed as a per cent of the MAC value following reserpine and AMPT treatment, was 18 per cent.

Weight loss was observed in the reserpine-treated (Group 3) as well as the reserpine- and AMPT-treated (Group 4) rats. In the former group, the average weight loss was 13.5 per cent ( $43.5 \pm 4.0$  g, mean  $\pm$  SEM) while in the latter group it was 8.5 per cent ( $27.4 \pm 2.9$  g).

The pH and the  $P_{aCO_2}$  were within the normal range in all rats except those rats treated with reserpine and AMPT. These rats (Group 4) were metabolically acidotic (mean pH = 7.24) with respiratory compensation (mean  $P_{aCO_2}$  of 25 mmHg). The administration of 2 mg/kg PCP, however, did not change their pH and produced only minimal changes in  $P_{aCO_2}$  (mean  $P_{aCO_2}$  of 28 mmHg). The  $P_{aO_2}$  was more than 150 mmHg in all the rats.

The average control value for the norepinephrine content of the hypothalamus was 1890 ng/n tissue. The control value was comparable to those reported earlier.<sup>16,17</sup> The norepinephrine content in the reserpine plus AMPT-treated rats was reduced markedly (<4 per cent of control) and was within the noise range of the chromatograph (<80 ng/g tissue).

### Discussion

PCP, in the doses used in this study, produces behavioral alterations in both humans as well as experimental animals without producing loss of consciousness. Several investigators have reported that in rats, PCP (2 to 16 mg/kg, ip) produces characteristic stereotyped behavior and a serotonergic syndrome.<sup>20,21</sup> Other groups have observed that in rats with unilateral lesions in the substantia nigra, PCP in the same dose ranges induces a dose-related ipsilateral rotation—an action shared by amphetamine.<sup>1-3</sup> Chronic PCP abusers (average  $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , intravenous) show violent self-destructive behavior, suicidal depression, and perform reckless acts which may result in the need for emergency operations.<sup>22</sup>

Behavioral, receptor binding and *in vitro* dopamine uptake studies suggest that PCP may have amphetamine and opiate agonist-like actions.<sup>5,23</sup> Our results, however, indicate that the effect of PCP on anesthetic requirement (MAC) is not mediated through either of the above-mentioned mechanisms. Johnston *et al.* have shown that acute administration of amphetamine increases MAC.<sup>9</sup> In contrast, PCP decreased cyclopropane MAC in a dose-related manner. Evidence from *in vivo* single-unit recordings of the dopaminergic cells of the substantia nigra in the rat brain also supports the view that the action of PCP is different from that of amphetamine. While amphetamine decreases the firing rate of dopaminergic substantia nigra cells, PCP increases the firing rate of a subpopulation of dopaminergic neurons.<sup>24</sup> Our observation that naloxone failed to alter the decrease in MAC produced by PCP indicates that an interaction of the drug with opiate mechanisms is unlikely.

Though earlier reports suggested that naloxone antagonized general anesthesia,<sup>25</sup> later studies have failed to show any significant effect of naloxone on anesthetic requirement.<sup>26-29</sup> In this study, we observed that naloxone, in a dose well above that necessary to antagonize the action of opiates or compete with enkephalins<sup>30</sup> at their receptors in rat brain, did not alter the MAC of cyclopropane. Our observations, therefore, would add further evidence to the view that the predominant action of inhalational anesthetics is not likely to be mediated via opiate receptor mechanisms.

Several lines of evidence suggest that central monoamines play an important role in the modulation of anesthetic requirement. Miller *et al.* observed that reserpine (1 mg/kg a day for 2 days) produced a 31 per cent decrease in halothane MAC in dogs.<sup>10</sup> Our observations of a 20 per cent decrease in cyclopropane MAC in reserpine-treated rats (Group 3) are similar to that of Roizen *et al.*<sup>16</sup> who found a 16 to 22 per cent decrease in cyclopropane MAC in rats following selective destruction of several brainstem areas containing serotonin or norepinephrine. However, our observations were at variance with those of Mueller *et al.* who did not observe any alteration of cyclopropane MAC in rats treated with a single high dose of reserpine (10 mg/kg, ip).<sup>18</sup>

Though weight loss was observed in both the reserpine and AMPT-treated rats due to diarrhea and dehydration, it is unlikely that the observed changes in MAC were due to their state of health. While the reserpine and AMPT-treated rats (Group 4) lost significantly less weight than the reserpine-treated group (Group 3), they had a more marked decrease in MAC (43 per cent in Group 4 *vs.* 20 per cent in Group 3).

In the doses administered in this study, reserpine produces a 75 per cent depletion of whole brain norepinephrine and dopamine (DiFazio CA: unpublished ob-

servations). Since depletion of catechols with reserpine is usually incomplete, we treated a group of rats with reserpine as well as a catecholamine synthesis inhibitor,  $\alpha$ -methyl-p-tyrosine.<sup>31</sup> Haeusler had shown that a 96–98 per cent depletion of catecholamines could be achieved in rats with the doses of reserpine and AMPT used in this study.<sup>14</sup> The profound depletion of catecholamines with reserpine and AMPT resulted in a marked (43 per cent) decrease in cyclopropane MAC in the rats in Group 4 of this study. This decrease is greater than the reduction in halothane MAC observed by Miller *et al.*<sup>10</sup> following the administration of  $\alpha$ -methyldopa, reserpine, or both  $\alpha$ -methyldopa and reserpine. Mueller *et al.* did not observe any change in cyclopropane MAC following AMPT treatment alone.<sup>13</sup> However, difference in methodology may explain some of the apparent discrepancies between our observations and those of Mueller *et al.* The rats in the study by Mueller and co-workers were anesthetized 30 min following a single ip injection of AMPT (250 mg/kg) and were not pretreated with reserpine. While AMPT prevents synthesis of catechols, it does not interfere with the release of the stores of catechols already present. Moreover, Spector *et al.* have shown that the peak effect of AMPT is observed eight hours following its administration.<sup>31</sup> It is therefore likely that only partial depletion of catechols was achieved by Mueller and co-workers. The results of our study add further evidence for an important role of central catecholaminergic neurotransmission in the action of general anesthetics.

The effect of PCP in the reserpine and the reserpine plus AMPT-treated groups indicates that while an effect on central monoamines may play a part in the mechanism of action of PCP, it is probably not the sole mode of action of the drug. In the rats in Group 3, we observed that the decrease in MAC produced by monoamine depletion with reserpine, and the administration of PCP (4 mg/kg, sc) were non-additive. In rats not pretreated with any drug, 4 mg/kg, PCP produced a 42 per cent decrease in MAC. However, in monoamine-depleted rats, the administration of the same dose of PCP resulted in only a 25 per cent reduction in MAC. This suggests that the action of PCP may in part be through a central monoamine mechanism. In rats given reserpine and AMPT where a high degree of catecholamine depletion was achieved, the ability of PCP to decrease MAC was reduced markedly but still not abolished. Thus, though an interaction of PCP with catecholaminergic neurotransmission is strongly suggested, it appears unlikely to be the sole mechanism of action of the drug.

Recent *in vivo* electrophysiologic studies in the rat have shown that PCP, like general anesthetics, produces a nonspecific depression of glutamate and acetylcholine-induced excitatory synaptic transmission in several brain regions including the hippocampal formation.<sup>32</sup> There-

fore, it is possible that the observed effect of PCP on MAC is secondary to a nonspecific depression of synaptic transmission in the central nervous system, an action common to several general CNS depressants.

In this study, though the effect of PCP was studied on the anesthetic requirement of cyclopropane, we would expect qualitatively similar changes with other anesthetics. Roizen *et al.* have shown that both cyclopropane and halothane have qualitatively similar effects on catecholaminergic content in pontine and forebrain nuclei. The effect of selective ablation of the locus coeruleus, a norepinephrine cell-body area, decreases the anesthetic requirement of both halothane and cyclopropane.<sup>19</sup> Both halothane and cyclopropane anesthesia are associated with selective increases in catecholamine levels in the nucleus accumbens, locus coeruleus, and central gray catecholamine areas.<sup>33</sup> Since our observations strongly suggest an interaction of PCP with catecholaminergic neurotransmission, we expect similar decreases in MAC with other anesthetics as well.

Though any attempt to relate to humans the doses used in this study in rats is difficult, our observations indicate that in doses that produce behavioral disturbances, PCP significantly decreases anesthetic requirement. Based on our observations in the rat, caution is advised in the anesthetic management of patients intoxicated with PCP, since their anesthetic requirement may be very much less than would be expected in the non-intoxicated state. Therefore, there is a significant potential for anesthetic overdose in the PCP-intoxicated patient.

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