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BRIEF COMMUNICATION

Phencyclidine: Effects on Motor Activity and Brain Biogenic Amines in the Guinea Pig

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JOHNSON, K. M., M. B. GORDON AND M. G. ZIEGLER. *Phencyclidine: Effects on motor activity and brain biogenic amines in the guinea pig.* PHARMAC. BIOCHEM. BEHAV. 9(4) 563–565, 1978.—Previous reports suggesting that the behavioral response of the guinea pig to phencyclidine (PCP) administration is more similar to the effects of PCP observed in higher animals than those observed in mice and rats prompted us to investigate the effects of PCP on spontaneous motor activity and brain biogenic amine levels in the guinea pig. Doses of 2.5 and 5.0 mg/kg PCP were found to significantly elevate spontaneous motor activity; however, 7.5 mg/kg PCP produced highly variable results which were not significantly different from control. The concentrations of tryptophan, serotonin, 5-hydroxyindoleacetic acid, and norepinephrine were measured in the forebrain and hindbrain of previously drug naive animals 30 min after administration of 5 mg/kg PCP. As compared to saline injected control animals, PCP was observed to have no effect on any of the neurochemical determinants measured. Contrary to previous reports, these data suggest that PCP produces behavioral effects in the guinea pig which are not unlike those observed in mice and rats. Furthermore, the effects which we report on spontaneous motor activity are not related to changes in the regional concentration of any of the neurochemical variables which were measured.

Phencyclidine (PCP) 5-Hydroxytryptamine Sernylan Norepinephrine Motor activity Guinea pig

PHENCYCLIDINE (PCP) is one of several 1-arylcyclohexamines which were developed originally as potential anesthetic agents. PCP, however, was withdrawn from clinical trials because it produced rather bizarre emergence reactions and, in fact, is currently approved only for veterinary use (Sernylan®, Bio-Ceutic Laboratories, Inc.). PCP possesses several properties which have led to its widespread use both as a primary drug of abuse and as an adulterant of other illicit drugs [1]. This drug possesses general anesthetic, psychomotor stimulant, and sedative-hypnotic properties in animals [2] and remarkable psychotomimetic properties in man [8].

Although several studies have investigated the effect of PCP on behavior and brain neurochemistry in the rat, there is some question about whether or not the rat is an appropriate animal model for such studies. This stems primarily from studies which showed that the effects of PCP varied markedly depending on the species used [2]. For example, PCP produced excitatory activity in mice and rats, as measured by actophotometers and jiggle cages, respectively, while producing a quieting and taming effect in higher species including the cat, dog, and monkey [2]. This study also determined that effects similar to those seen in the monkey were also observed in the guinea pig and hamster. Because of the apparent similarities between the effects of PCP produced in the guinea pig and monkey we decided to investigate the effect of PCP on the spontaneous motor activity of the guinea pig using a measure similar to that used to investigate the motor activity of mice and rats in the study mentioned above [2]. Since there are reports suggesting the involvement of certain biogenic amines in the mediation of PCP effects in the rat, we also measured the effects of PCP on brain norepinephrine (NE), tryptophan, 5-hydroxytryptamine (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA).

METHOD

Spontaneous Motor Activity

Male albino guinea pigs weighing 400–600 g were used in all experiments and were housed in groups of 3 under a 12:12 light-dark cycle with food and water available at all times. Two groups of 5 guinea pigs were used in these experiments. Activity was measured for 1 hr periods using circular alley cages 30 cm in dia. with 8 cm wide circular runways [9]. Four equally spaced 2.5 cm panels in the floor of each cage activated microswitches connected to an electromechanical counter. Results are expressed as counts/hr. Because guinea pigs tend to freeze in a novel environment, each animal was placed in the activity chamber for 1 hr each day until a stable baseline was reached. This required about 3 weeks. During this habituation period we determined that there was no difference in spontaneous motor activity between morning and afternoon sessions, but there was considerable variance in activity between animals. Therefore, each animal was injected (SC) with saline in the morning and PCP (Sernylan) in

the afternoon. Activity was measured between 15 and 75 min after each injection. At least 3 days were allowed to elapse between the testing of various doses of PCP. Group 1 animals were given 2.5, 5.0 and 7.5 mg/kg PCP on Days 1, 4, and 8, respectively, while the order was reversed for Group 2. Statistical comparisons were made using the paired *t*-test.

Biochemical Analysis

Two groups of drug naive guinea pigs obtained from the same source were used in this experiment. Either saline or 5 mg/kg PCP (Sernylan) was injected (SC; 1 cc/kg) and the animals were sacrificed by decapitation 30 min later. The brain was rapidly removed, the cerebellum discarded, and the forebrain separated from the brainstem by a section just anterior to the superior colliculi on the dorsal aspect, and just anterior to the mammillary bodies on the ventral aspect. The brain sections were rapidly homogenized in 0.4 N perchloric acid and centrifuged at 10,000×g for 10 min. An aliquot of 50 μl of the supernatant was frozen for the subsequent analysis of NE by a sensitive radioenzymatic assay [6]. Tryptophan, 5-HT, and 5-HIAA were separated from the remainder of the supernatant by ion-exchange chromatography [5]. Fluorometric assays were used to quantitate tryptophan [4] and 5-HT and 5-HIAA [3]. Statistical comparisons were made by the use of Student's *t*-test.

RESULTS AND DISCUSSION

The data in Table 1 show the effects of PCP on the spontaneous motor activity of both groups of guinea pigs. It can be seen that 2.5 mg/kg resulted in substantial increases in motor activity (225–345%) and 5.0 mg/kg PCP produced even more dramatic increases (835–875%). Increased motor activity was observed in every animal tested after either 2.5 or 5.0 mg/kg PCP, with the minimum response of an individual animal being twice saline values. This is in sharp contrast to the effects produced by 7.5 mg/kg PCP. Of the 10 animals tested at this dose, PCP produced a 6 to 10 fold increase in 4 of the animals, an 80–85% decrease in 3 animals, and no appreciable change in the activity of the other 3. Although ataxia was observed at all 3 dose levels, it was most severe at 7.5 mg/kg. The heterogeneous nature of the effects of 7.5 mg/kg PCP may be the result of a dose level which just produces sufficient ataxia to overcome the psychomotor stimulant effects of the drug. Significant ataxia (as measured by Rotarod performance) has been previously demonstrated in mice at doses which increased motor activity [2]. The results of this study on the guinea pig and those previously reported on the rat differ only in that PCP produced a linear dose-response curve in rats rather than an inverted-U shaped curve as observed here. Since these studies used the same dose range, we can only conclude that the guinea pig appears to be more sensitive to the ataxic effects of PCP than the rat.

Since in Group 1 7.5 mg/kg PCP was administered last and 3 of the 5 animals responded with nearly 10 fold increases in activity, it may be argued that this observation may indicate development of tolerance to the ataxic effects of PCP. Although this may be the case, it is clear that a more systematic investigation of this possibility would have to be carried out in order to address this argument.

The data represented in Table 2 are the results of one experiment in which the effects of 5 mg/kg PCP on forebrain and brainstem NE, tryptophan, 5-HT, and 5-HIAA were assessed. No significant effects of PCP were observed. To our knowledge this is the only study which has measured the effects of PCP on any neurochemical variables in the guinea pig brain. However, several studies have examined the effects of 10 mg/kg PCP on these parameters in the rat brain. For example, depending upon the strain used, both increases and decreases have been observed in both 5-HT and 5-HIAA whole brain concentrations [10]. Investigators have also observed a PCP-induced decrease of brain tryptophan [11] and brain NE [7]. Since the data from this study do not show similar changes we conclude that the effects of 5 mg/kg PCP which we observed on spontaneous motor activity are not correlated with either forebrain or brainstem changes in the concentration of NE, tryptophan, 5-HT, or 5-HIAA. This, of course, does not rule out the involvement of either serotonergic or noradrenergic systems in the mediation of the effects of PCP. It is entirely possible that PCP may alter NE or 5-HT synthesis and metabolism without altering the steady-state concentration of either.

As alluded to earlier, the primary reason for doing this

TABLE 1

EFFECT OF PCP ON SPONTANEOUS MOTOR ACTIVITY

Treatment	Counts/hr ± SEM Group 1	Group 2
Saline	23 ± 4	45 ± 8
2.5 mg/kg	75 ± 16*	199 ± 69
Saline	29 ± 7	39 ± 3
5.0 mg/kg	356 ± 95*	381 ± 55*
Saline	29 ± 7	59 ± 14
7.5 mg/kg	174 ± 80	58 ± 32

On each test day, rats were injected (SC) with saline in the morning and the indicated dose of PCP in the afternoon. Activity was measured between 15 and 75 min after injections. N = 5 for each group.

*$p < 0.05$.

TABLE 2

NEUROCHEMICAL EFFECTS OF PCP

	ng/g (Mean ± SEM) Saline	PCP
Forebrain		
NE	124 ± 10	133 ± 19
Tryptophan	673 ± 76	593 ± 24
5-HT	131 ± 22	153 ± 26
5-HIAA	119 ± 3	111 ± 10
Brainstem		
NE	134 ± 16	118 ± 15
Tryptophan	1869 ± 148	1772 ± 61
5-HT	298 ± 56	239 ± 19
5-HIAA	478 ± 35	523 ± 24

Rats were administered either saline or 5 mg/kg PCP (SC) and sacrificed 30 min later. Saline N = 5; PCP N = 4.

study was to ascertain whether or not future behavioral or neuropharmacological studies of PCP utilizing the guinea pig could be better correlated with studies in higher species than studies using the rat. It is our conclusion that the guinea pig would afford no such advantage.

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