Pharmacology Biochemistry & Behavior, Vol. 12, pp. 761–766. Printed in the U.S.A.

Modification of the Behavioral Effects of Phencyclidine by Repeated Drug Exposure and Body Weight Changes[1]

WILLIAM L. WOOLVERTON,[2] BILLY R. MARTIN AND ROBERT L. BALSTER

Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298

Received 20 July 1979

WOOLVERTON, W. L., B. R. MARTIN AND R. L. BALSTER. *Modification of the behavioral effects of phencyclidine by repeated drug exposure and body weight changes*. PHARMAC. BIOCHEM. BEHAV. 12(5) 761–766, 1980.—In the first experiment, the effects of phencyclidine (PCP) on intake of sweetened condensed milk by rats were compared before and during a period of repeated daily injections of PCP or saline. A shift to the right in the PCP dose-effect function was found in rats receiving daily PCP injections indicating tolerance development to the effects of PCP on milk intake. The dose-effect function of PCP was shifted to the right in animals receiving daily saline as well. However, when body weight changes were controlled for in this groups of animals, the effects of PCP were the same as they had been initially, implicating body weight as a determinant of the behavioral effects of PCP. In the second experiment, a direct comparison of the behavioral effects of PCP in high- and low-weight animals revealed diminished effects of PCP in high-weight animals. When these animals were treated with ^{3}H-PCP, brain total radioactivity as well as ^{3}H-PCP in the high-weight animals were significantly lower than those in the low-weight animals.

Phencyclidine Tolerance Behavioral effects Rats Body weight Pharmacokinetics Tissue localization

THE recent emergence of phencyclidine (PCP) as a drug of abuse has led to increasing interest in the behavioral and toxicological effects of repeated administration of the drug. Several investigators [3, 10, 13, 15] have reported tolerance to the behavioral effects of PCP in the mouse, rat, and squirrel monkey during periods of repeated drug administration ranging from 6 to 126 days. The effects of daily injections of PCP gradually diminished during chronic administration, and, where complete PCP dose-effect functions have been compared before and during chronic administration, roughly 2-fold shifts to the right have been observed [3,15].

The first experiment was designed to evaluate the development of tolerance to the effects of PCP on an appetitive behavior, the intake of sweetened milk by rats. Tolerance development to the effects of a number of drugs has been examined using this procedure [2, 7, 12, 16] and the results have been comparable to those found using other behavioral tests. We found PCP tolerance similar to that reported in other studies of chronic PCP administration, but the extent of tolerance development was affected by weight changes in the chronic treatment and control groups. In a second experiment, brain levels of radioactivity were correlated with the effects of the drug on milk intake in rats of different body weights. Body weight was found to have an important influence on the behavioral effects of PCP, and on the distribution of PCP to the brain.

EXPERIMENT 1

METHOD

Animals and Apparatus

The animals were 18 experimentally naive male Sprague-Dawley derived DUB rats (Flow Laboratories, Dublin, VA) that weighed between 200 and 285 g at the beginning of the experiments. They were individually housed in steel mesh cages (18×19×25 cm) where water was continuously available. For 15 min each day a solution of milk (2 parts tap water to 1 part Borden's Sweetened Condensed Milk) was placed on the front of each cage in 50 ml plastic centrifuge tubes equipped with standard rubber stoppers and drinking spouts. In addition, each rat was given 4–6 g of rat chow (Rodent Lab Chow, Ralston Purina Co., St. Louis, MO) after each test session. Food was left in the cage until consumed.

Procedure

Experimental sessions consisted of 15 min access to the milk solution in the drinking tubes. Sessions were conducted in the home cages at the same time each day, seven days a week. Initially, all rats were given IP injections of 0.9% saline 15 min before the session for five randomly spaced

[1]Supported by NIDA Grant DA-01442
[2]Post-Doctoral Fellow supported by NIDA Grant T32-DA-07027.

sessions to allow adaptation to the injection procedure. When milk intake stabilized for the group (less than 10% variation in mean intake for 3 consecutive sessions) the animals were divided into 2 groups of 9 rats each that were matched for body weight and milk intake. PCP dose-effect functions were then determined in both groups. Test doses of PCP (1.0–8.0 mg/kg) were administered in an ascending order 15 min before experimental sessions. Drug treatments were separated by at least three non-drug sessions with stable milk intake.

Following the determination of the effects of single injections of PCP on milk intake, the daily injection regimen was begun. For one group of animals, a dose of PCP (4.0 mg/kg) that decreased intake to less than 50% of control levels without totally eliminating drinking was administered daily for 36 consecutive sessions. The daily injection dose of PCP was then increased to 8.0 mg/kg for an additional 56 sessions. The other group of animals received injections of 0.9% saline (1 mg/kg) during this period with all injections given 15 min before the session. During the chronic dosing period, animals given 8.0 mg/kg PCP frequently drank little or no milk during the experimental session and, consequently, lost weight. If the body weight of any individual animal fell below 200 g, the milk solution was left on that subject's cage for an additional 2–3 hours to prevent death by starvation.

Between sessions 73 and 92 the dose-effect function of PCP on milk intake was redetermined in both groups of animals in the same manner as it had been determined initially. Test doses of PCP (1.0–12 mg/kg) were administered in an ascending order 15 min before the session, instead of the usual injection. At least 3 sessions in which animals received their usual injection of 8.0 mg/kg PCP or saline intervened between test doses of PCP. Animals received only the test dose of PCP on dose-effect sessions.

Following this redetermination of the PCP dose-effect function, the mean body weight of the control group was 352.8 g, while the animals in the drug-treated group weighed an average of 256.6 g. For the next 35 sessions, saline control animals continued to receive daily injections of saline, followed in 15 min by the mean amount of milk consumed by the drug-treated group during the period of daily administration of 8.0 mg/kg PCP (approximately 12 ml). Conversely, the drug-treated group continued with daily injections of 8.0 mg/kg PCP followed in 15 min by 50 ml of milk which they were allowed 3 hours to consume. Volume intake was recorded at the end of 15 min for this group and the milk replaced on the cages. This modified pair-feeding procedure was continued until body weight conditions were reversed, i.e. the animals receiving daily PCP weighed approximately 350 g while the animals receiving daily saline weighed approximately 250 g. This procedure was used to control for possible changes in the behavioral effects of PCP that may have resulted from body weight changes rather than repeated drug or saline injections. Between sessions 22–35 of pair-feeding, dose-effect functions of PCP were redetermined exactly as in previous dose-effect determinations.

Individual volume of milk intake was recorded at the end of each experimental session, and group means and standard errors calculated. The effects of PCP on mean milk intake (ml) are presented.

RESULTS

PCP Dose-Effect Determinations

Following vehicle injections, rats in the drug group drank an average of 27.5 ml of milk, while those in the saline group drank 25 ml during the 15 min experimental sessions (Fig. 1A and 1B). The effects of single injections of PCP on milk intake were initially the same for both groups. PCP (1.0–8.0 mg/kg) produced a dose-related decrease in milk intake in both groups. In addition, the highest doses (4.0 and 8.0 mg/kg) produced repeated circling and ataxia in all rats. When the dose-effect function was redetermined during daily PCP administration, PCP again produced a dose-related decrease in milk intake in the drug group, but the effect of each dose on intake was less than it had been initially, indicating tolerance development (Fig. 1A). However, in the group receiving daily saline injections, PCP (1.0–4.0 mg/kg) had no effect on intake and 8.0 mg/kg only slightly decreased intake when the effects of these doses were redetermined (Fig. 1B). In addition to the observation that these animals drank more milk than animals that had received PCP daily, there was also less overt circling and ataxia after 8.0 mg/kg PCP. Thus, the control animals were also less sensitive to PCP than they had been initially. We hypothesized that this decreased sensitivity to PCP in control animals may have been due to the large weight gain in these animals relative to the drug-treated group (Fig. 2). When the body weights of the control animals were reduced to their original levels (250 g) by restricting milk intake, the then redetermined dose-effect function was not different from the original, i.e., there was no decrease in sensitivity to PCP (Fig. 1B). In addition, when the mean body weight of the drug group was increased to the level of the saline group (350 g) the dose-effect redetermination was shifted even farther to the right (Fig. 1A). These data suggest an influence of body weight on the behavioral effects of PCP.

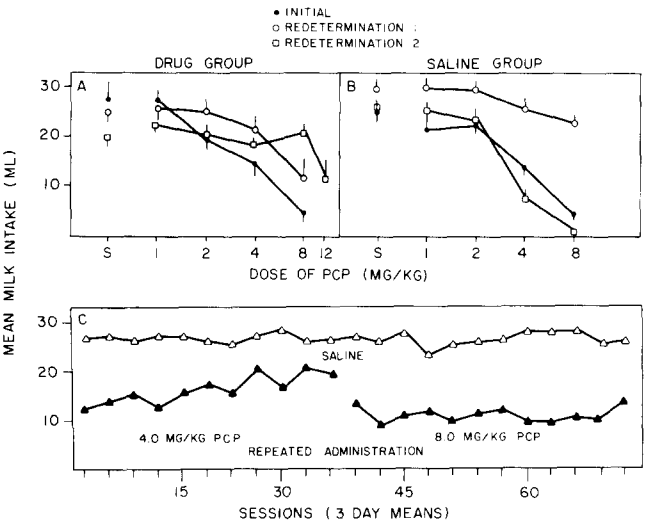

FIG. 1.A. Effects of single injections of PCP on the milk intake of rats (n=9) before and during a period of daily injections of PCP. ●-Initial dose-effect determination. ○-First dose-effect redetermination. □-Second dose-effect redetermination, after modified pair-feeding. The points above S represent the effects of saline injection during each dose-effect determination. Vertical lines are the standard error of the mean. 1.B. Same as above, for rats (n=9) receiving daily injections of saline. 1.C. The effects of daily injections of PCP (4.0 or 8.0 mg/kg) or saline on milk intake of rats. Each point is the mean of 3 successive sessions.

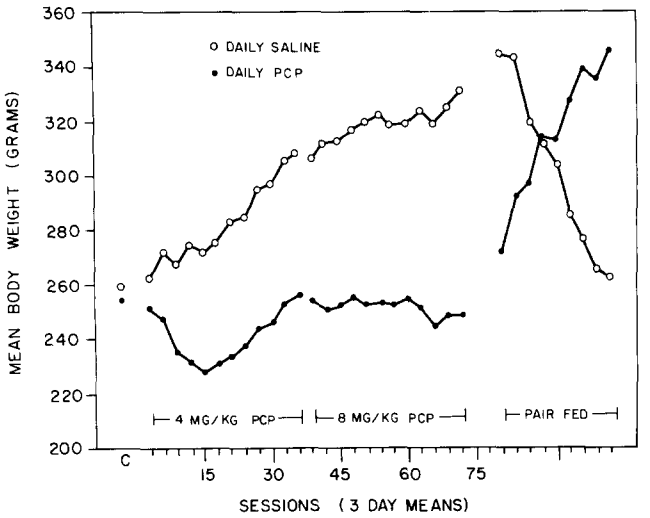

FIG. 2. Effects of daily injections of PCP (4.0 or 8.0 mg/kg) or saline on the average body weight of rats allowed to drink condensed milk. The points above C represent the body weights of the two groups of animals under control conditions at the beginning of the experiments. The effects of the modified pair-feeding procedure on body weight are shown in the right portion of the graph.

Effects of Repeated PCP Administration

When 4.0 mg/kg PCP was administered before the session for 36 consecutive sessions, milk intake increased from an average of 12 ml for sessions 1–3 to 19.5 ml for sessions 34–36 (Fig. 1C). When the daily injection dose was increased to 8.0 mg/kg, intake was reduced to an average of 13.5 ml and there was no change in the effect of this dose during the remainder of the daily injection regimen. Intake for the saline control group remained at control levels for the duration of this period.

Figure 2 presents the body weights for the two groups of animals. For the first 15 sessions of daily injections with 4.0 mg/kg PCP, mean body weight of the drug group decreased by about 23 g, and increased thereafter. When the daily injection was increased to 8.0 mg/kg, mean body weight was the same as when injections of 4.0 mg/kg were begun, and decreased slightly during the period of daily injections of 8.0 mg/kg PCP. In contrast, the average body weight of the saline control animals increased from 258 g to 330.5 g at the end of the injection regimen.

EXPERIMENT 2

Diminution of the effects of PCP on milk intake in the saline control group when their body weights were high, and loss of this effect when body weights were reduced to original levels, strongly suggested that body weight was an important determinant of the effects of PCP. PCP has been shown to be highly lipophilic [6] and it may be preferentially stored in adipose tissue after IP administration in rats [5]. Therefore it was possible that higher brain levels of PCP were achieved in lean animals with little adipose tissue. To test this hypothesis, an additional experiment was designed to compare the effects of single injections of PCP on milk intake in two groups of rats differing in body weight, and to compare the distribution of radiolabelled PCP to the brains and other tissues of these subjects.

METHOD

Animals and Apparatus

The animals were 18 experimentally naive male rats of the same strain and initial weight range as those used in Experiment 1. The apparatus was the same as that used in Experiment 1.

Procedure

The animals were divided into two groups of nine subjects each. One group (low-weight group) was given daily feedings of milk (10–15 ml) adjusted to maintain the mean body weight of the group at approximately 250 g, while the second group (high-weight group) was allowed 3 hours access per day to unlimited amounts of the milk solution. When the mean body weight of the high-weight group reached 350 g (90 sessions), dose-effect functions of PCP were determined in both groups of animals with doses of PCP tested in an ascending order and separated by at least 3 drug-free days. The dose-effect function of PCP was redetermined in both groups beginning 75 days later (Session 165), exactly as initially, with body weights maintained during the intervening period by adjusted feedings of the milk solution or rat chow. The constraint that milk intake be within 10% of original control levels for the two sessions preceding a test dose of PCP was in effect for the dose-effect redetermination.

Ten sessions after completion of the redetermination of the dose-effect function of PCP, all animals were injected with ^{3}H-PCP (10 μCi/4.0 mg/kg) 15 min before the 15 min experimental session and were decapitated immediately after the session. Blood from the cervical wound was collected in heparinized glass tubes and centrifuged at 1000 g for 20 min to obtain plasma. Duplicate plasma aliquots (50 μl) were added to scintillation fluid composed of two parts toluene containing 0.4% diphenyloxazole and 0.01% 1,4-bis(2-(4-methyl-5-phenyloxazolyl) benzene) and one part triton X-100. Radioactivity was quantitated by liquid scintillation counting and efficiency was established by external standardization. Brain (dissected in half), and samples from lung, heart, liver lobe, right kidney and epididymal fat, were weighed and placed in oxidation cups. Intestines (large and small intestines plus feces) were homogenized in 4 volumes of water with a polytron (Brinkmann Instruments) and 0.5 ml aliquots added to oxidation cups. All samples were oxidized to ^3H_2O using a Packard Tri-Carb sample oxidizer (efficiency>95%) and radioactivity determined by liquid scintillation spectrometry. The radioactivity (dpm's/g tissue) was divided by the specific activity of the ^{3}H-PCP in order to express the data as PCP equivalents/g tissue.

In order to determine whether or not the metabolism of ^{3}H-PCP differed between the two treatment groups, radioactivity was extracted from plasma and brain, and ^{3}H-PCP was distinguished from its metabolites by thin-layer chromatography (TLC). For the extraction, one-ml aliquots of plasma and brain homogenates were pooled for each group and radioactivity extracted by shaking the pooled samples three times with methanol (7 ml each). The methanol extracts of each sample were pooled, evaporated to dryness, and reconstituted with one ml of methanol. Greater than 80% of the radioactivity was recovered from all tissues. Over 90% of ^{3}H-PCP was extracted from a tissue blank using the procedure described above. Aliquots of the sample extracts were applied as a band on 5×10 cm silica gel plates along with 15 μg each of PCP, 1-(1-phenylcyclohexyl)-4-hydroxypiper-

idine (P-4-OH-PCP) and 4-phenyl-4-piperidinocyclohexanol (C-4-OH-PCP). The plates were developed with chloroform: methanol: concentrated ammonium hydroxide (90:10:1), and the references were visualized by exposing the plates to iodine vapor. Each plate was divided into 6 bands. Band one was above ^{3}H-PCP; band 2 corresponded to ^{3}H-PCP (R_f 0.75); bands 3 and 4 contained P-4-OH-PCP and C-4-OH-PCP, respectively; band 5 was just above the origin (band 6). All bands were scraped into scintillation vials containing 0.5 ml methanol and sonicated for 30 min before the addition of 10 ml of scintillation fluid for liquid scintillation spectrometry. The radioactivity in each band was expressed as a percentage of the total radioactivity on the plate.

Data Analysis

Milk intake data were compared as in the first experiment. In Experiment 1, the effects of body weight that were of interest were seen in the dose-effect redetermination within the group of animals that had received daily saline injections. Consequently, in Experiment 2 similar comparisons were made between groups using data from dose-effect redeterminations. Dose-effect redeterminations were not systematically different from initial dose-effect determinations in either group, and between group differences were similar to those presented here. Tissue levels of PCP were compared using a two-tailed *t*-test for unpaired samples, and linear regression analyses were performed on body weight, milk intake and brain levels of radioactivity using individual animal data.

RESULTS

The results of the redetermination of the PCP dose-effect functions in light and heavy animals are shown in Fig. 3. Consistent with the results in Experiment 1, PCP produced a dose-related decrease in milk intake. Further, the effects of PCP on milk intake were less in the high-weight group (mean body weight=345.6 ± 9.8 SEM) than in the low-weight group of animals (mean body weight=246.9 ± 12.8 SEM).

Following injections of ^{3}H-PCP (4.0 mg/kg) milk intake was again higher in the high-weight animals (mean of 24.0 ml vs 20.2 ml). The tissue distribution of radioactivity is presented in Table 1. All tissues of the low-weight group, with the exception of intestines, contained higher concentrations of radioactivity than did those of the high-weight group. The concentrations of radioactivity in intestines, kidney, heart and brain were significantly different between the two groups. The brain levels of ^{3}H-PCP plus its metabolites in the low-weight group were almost twice those in the high-weight group, the difference being significant at the 0.05 level. Linear regression analysis revealed a significant ($p<0.05$) negative correlation (r=−.57) between body weight and brain levels of radioactivity as well as a significant ($p<0.05$) negative correlation (r=−.55) betwen milk intake and brain levels of radioactivity.

Radioactivity was extracted from plasma and brain of each group and analyzed by TLC to determine actual ^{3}H-PCP levels. TLC analysis of the plasma extracts revealed no differences between the two treatment groups. Plasma radioactivity from the low-weight group corresponded to PCP (20%), P-4-OH-PCP (6%), C-4-Oh-PCP (8%), and the TLC origin (63%), while that in the high-weight group was 23, 11, 6 and 56%, respectively. The brain radioactivity in the low-weight group was mostly PCP (52%) with 19, 6 and 12% attributed to P-4-OH-PCP, C-4-OH-PCP and the origin, respectively. The brain radioactivity in the high-weight group differed only slightly from the low-weight group in that 43% of the radioactivity corresponded to PCP, 17% to P-4-OH-PCP, 9% to C-4-OH-PCP and 21% to the origin. When the percentage of radioactivity corresponding to PCP is multiplied by the tissue concentration of radioactivity (PCP equivalents), the mean plasma levels of ^{3}H-PCP are 201 and 197 ng/ml for the low-weight and high-weight groups, respectively. The mean brain levels of ^{3}H-PCP were calculated to be 523 and 228 ng/g for the low-weight and high-weight groups, respectively.

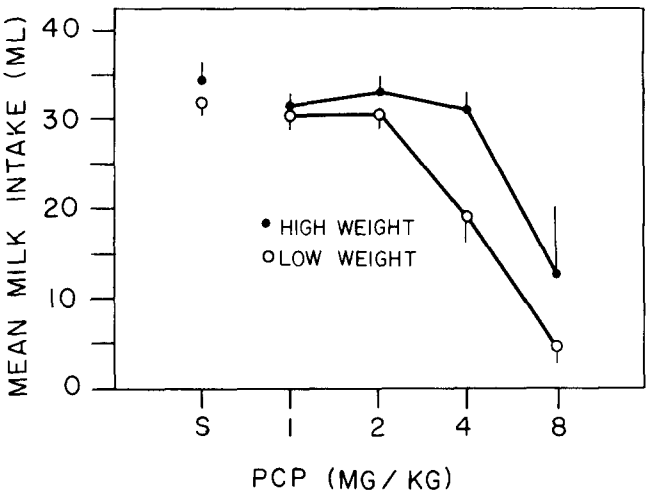

FIG. 3. Effects of single injections of PCP on milk intake of rats in the high-weight (●-mean body weight=345.6 g) and the low-weight (○-mean body weight=246.9 g) animals. The points above S represent the effects of saline injection and vertical lines are the standard error of the mean.

TABLE 1

LOCALIZATION OF RADIOACTIVITY IN HIGH WEIGHT AND LOW WEIGHT RATS AFTER AN IP INJECTION OF ^{3}H-PCP

	PCP equivalents (ng/g or ml)*	
Tissue	High weight (N=7)	Low weight (N=9)
Intestine	23,127 ± 1,667†	18,710 ± 664
Liver	17,466 ± 1,623	19,515 ± 1,585
Kidney	6,920 ± 535	12,259 ± 1,765‡
Lung	4,151 ± 303	5,872 ± 776
Epididymal fat	3,975 ± 1,493	4,186 ± 1,063
Heart	1,294 ± 84	3,362 ± 468§
Brain	544 ± 17	1,005 ± 142†
Plasma	855 ± 88	1,005 ± 139

*Data expressed as mean ± SE and analyzed by Student's *t*-test.
†$p<0.05$.
‡$p<0.01$.
§$p<0.005$.

DISCUSSION

As with other drugs [2, 7, 12, 16], PCP produced a dose-related decrease in milk intake of rats when given 15 min before access to milk. The effective dose range for disruption of milk intake (1.0–8.0 mg/kg) was the same as the effective

dose range for disruption of fixed-interval responding in rats [15] indicating that this procedure may be as sensitive to PCP-induced behavioral disruptions as are more complex schedule-controlled behaviors in rats. In comparison to other laboratory species, the behaviorally effective dose range of PCP for the rat is about 1/10 that of the squirrel monkey [3] and rhesus monkey [1]. The roughly two-fold shift in the PCP dose-effect function in animals receiving daily PCP injections is of a magnitude comparable to that reported in other studies of PCP tolerance development [3,15]. As pointed out by Chait and Balster [3], the magnitude of tolerance to the behavioral effects of PCP is considerably less than has been found for other psychoactive drugs such as methamphtamine [4] or Δ^9-THC [8]. The consistent two-fold shift in the PCP dose-effect function, even with injection regimens involving 4 daily injections and/or high doses, suggest that this may be the limit of tolerance to the behavioral effects of PCP. Nevertheless, it is possible that greater tolerance could be engendered by a more frequent injection regimen.

When 4 mg/kg PCP was administered before experimental sessions for 36 consecutive daily sessions, milk intake increased from less than 50% of control levels to about 77% of control levels. These results are comparable to those collected in similar test situations with cocaine, *d*-amphetamine, methylphenidate and fenfluramine [2, 7, 12, 16]. However, when the daily injection dose of PCP was increased to 8.0 mg/kg, no attenuation of the effects of this dose was found over a period of 36 additional sessions. These data are consistent with the results of Chait and Balster [3] who reported that tolerance failed to develop to the effects of a high dose of PCP given repeatedly to squirrel monkeys. However, the present results are in contrast to the findings of Woolverton and Balster [15] who reported tolerance development to the effects of 8.0 mg/kg PCP on fixed-interval responding in rats. This difference may be related to the difference in the duration of the experimental sessions in these two experiments. In the present experiment, experimental sessions were 15 min long, while in the experiment of Woolverton and Balster [15] sessions lasted 30 min. Since at least part of the tolerance to the behavioral effects of PCP can be accounted for by a reduction in the duration of action [3], it is possible that a 15 min experimental session is too brief to reveal this effect.

Surprisingly, a much larger shift to the right in the PCP dose-effect function was found in animals given daily injections of saline. The loss of this "tolerance" when body weights were decreased to original levels, as well as a direct comparison of the effects of PCP between groups of high- and low-weight animals revealed diminished behavioral effects of PCP in high-weight animals. It appeared that the diminished behavioral effects of PCP in the high-weight animals was due to lower brain levels of PCP. There are several possible explanations for the lower levels of ^{3}H-PCP this group of rats. It is possible that ^{3}H-PCP was sufficiently lipid soluble to be sequestered in the fat of high-weight animals, especially when given by intraperitoneal injection. Since the concentrations of radioactivity in epididymal fat were similar for both groups, the total amount of radioactivity in fat would be much greater in the high-weight rats (low-weight rats had little fat). PCP has recently been reported [9] to have a relatively long sojourn in adipose tissue of rats, lending support to the notion that differences in amounts of adipose tissue may have contributed to the differences in PCP pharmacokinetics in these two groups of rats. Further, adipose tissue in rats has been found to contain substantial amounts of *d*-amphetamine following repeated administration of the drug [14]. It is important to note, however, that in the case of cocaine, a highly lipid-soluble drug [11], no difference was found in the effects on milk intake when these effects were compared in high- and low-weight animals [16].

Differences in the distribution of radioactivity to other tissues were also seen between high- and low-weight subjects. With the exception of intestines, low-weight subjects had higher concentrations of radioactivity in all tissues examined, with the differences in kidney, heart and brain reaching statistical significance. In addition to the possibility that ^{3}H-PCP or metabolites are stored in the fat of the high-weight subjects, it is also possible that elimination via the intestines was greater in the high-weight animals since intestinal levels are higher than in the low-weight animals. Other changes in the pharmacokinetics of PCP, e.g. metabolic changes, could result from changes in nutritional state.

In conclusion, about two-fold tolerance develops to the effects of PCP on milk intake in rats. It is clear, however, that the behavioral effects of PCP can also be modified by changes or differences in body weight. The effects of PCP are diminished in high-weight vs low-weight subjects, and this difference in sensitivity can be accounted for at least in part by differences in brain levels seen between these subjects. There was a direct relationship between brain level and behavioral effects of ^{3}H-PCP. It is possible that this difference in behavioral sensitivity and PCP pharmacokinetics may be due to differences in relative amounts of adipose tissue in high-weight and low-weight subjects which might serve as a storage depot for PCP and reduce the amounts distributed to other tissues, including brain. This hypothesis requires additional research support before it can be accepted.

REFERENCES

1. Brady, K. T., R. L. Balster, L. T. Meltzer and D. Schwertz. Comparison of phencyclidine and three analogues on fixed-interval performance in rhesus monkeys. *Fedn Proc.* **38**: 256, 1979.
2. Carlton, P. L. and D. L. Wolgin. Contingent tolerance to the anorexigenic effects of amphetamine. *Physiol. Behav.* **7**: 221–223, 1971.
3. Chait, L. D. and R. L. Balster. The effects of acute and chronic phencyclidine on schedule-controlled behavior in the squirrel monkey. *J. Pharmac. exp. Ther.* **204**: 77–87, 1978.
4. Fischman, M. W. and C. R. Schuster. Tolerance development to chronic methamphetamine intoxication in the rhesus monkey. *Pharmac. Biochem. Behav.* **2**: 503–508, 1974.
5. James, S. H. and S. H. Schnoll. Phencyclidine: Tissue distribution in the rat. *Clin. Tox.* **9**: 573–582, 1976.
6. Kalir, A., S. Maayani, M. Rehavi, R. Elkavets, I. Pri-Bar, O. Buckman and M. Sokolovsky. Structure activity relationships of some phencyclidine derivatives: in vivo studies in mice. *Eur. J. med. Chem.* **13**: 17–24, 1978.
7. Kandel, D. A., D. Doyle and M. W. Fischman. Tolerance and cross-tolerance to the effects of amphetamine, methamphetamine and fenfluramine on milk consumption in the rat. *Pharmac. Biochem. Behav.* **3**: 705–707, 1975.
8. McMillan, D. E., W. L. Dewey and L. S. Harris. Characteristics of tetrahydrocannabinol tolerance. *Ann. N.Y. Acad. Sci.* **191**: 83–99, 1971.

9. Misra, A. L., R. B. Pontani and J. Bartolomeo. Persistence of phencyclidine (PCP) and metabolites in brain and adipose tissue and implications for long-lasting behavioral effects. *Res. communs chem. pathol. Pharmac.* **24:** 431–445, 1979.
10. Murray, T. F. The effects of phencyclidine on operant behavior in the rat: biphasic effect and tolerance development. *Life Sci.* **22:** 195–202, 1978.
11. Nayak, P. K., A. L. Misra and S. J. Mule. Physiological disposition and biotransformation of H^3-cocaine in acutely and chronically treated rats. *J. Pharmac. exp. Ther.* **197:** 556–569, 1976.
12. Pearl, R. and L. S. Seiden. The existence of tolerance to and cross-tolerance between *d*-amphetamine and methylphenidate for their effects on milk consumption and differential reinforcement of low rate performance. *J. Pharmac. exp. Ther.* **198:** 635–647, 1976.
13. Pinchasi, I., S. Maayani and M. Sodolovsky. On the interaction of drugs with the cholinergic nervous system. I. Tolerance to phencyclidine derivatives in mice: Pharmacological characterization. *Psychopharmacology* **56:** 27–36, 1978.
14. Sparber, S. B., S. Nagasawa and K. E. A. Burkland. A mobilizable pool of *d*-amphetamine in adipose after daily administration to rats. *Res. communs chem. pathol. Pharmac.* **18:** 423–431, 1977.
15. Woolverton, W. L. and R. L. Balster. Tolerance to the behavioral effects of phencyclidine: The importance of behavioral and pharmacological variables. *Psychopharmacology* **64:** 19–24, 1979.
16. Woolverton, W. L., D. A. Kandel and C. R. Schuster. Tolerance and cross-tolerance to cocaine and *d*-amphetamine. *J. Pharmac. exp. Ther.* **205:** 525–535, 1978.