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Interactions of Clonidine With Phencyclidine and Ketamine: Studies of Radial Maze Performance and Righting Reflex in Rats

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McCANN, D. J., R. A. RABIN AND J. C. WINTER. *Interactions of clonidine with phencyclidine and ketamine: Studies of radial maze performance and righting reflex in rats.* PHARMACOL BIOCHEM BEHAV **26**(1) 23–28, 1987.—Rats were trained to obtain food pellets in an 8-arm radial maze until a criterion of 89% efficiency, i.e., all arms entered within 9 arm entries, was reached in 5 consecutive sessions. Decreases in efficiency caused by phencyclidine (PCP; 4 to 9 mg/kg, IP, 15 min before testing) or ketamine (25 mg/kg, IP, 5 min) were attenuated when subjects were pretreated with clonidine (0.05 mg/kg, IP, 30 min). However, significant improvements in performance in the maze were not observed when clonidine (0.05 to 0.4 mg/kg, IP) was administered 15 min after PCP (9 mg/kg, IP, 45 min). Subsequent studies of righting reflex demonstrated an increased frequency and duration of anesthesia when clonidine (0.05 mg/kg, IP) was administered 15 minutes before PCP (12.5 to 50 mg/, IP) or ketamine (50 to 100 mg/kg, IP). When clonidine (0.05 mg/kg, IP) was administered 15 minutes before [^{3}H]PCP (40 μCi/kg, IP), brain levels of tritium were reduced by 42 to 55%. The present findings do not support the suggestion that clonidine may be useful in the treatment of PCP intoxication. The data do indicate that pretreatment of surgical patients with clonidine may reduce the dose of ketamine required for anesthesia.

Clonidine Phencyclidine (PCP) Ketamine Radial maze Righting reflex Anesthesia

INITIAL clinical trials of phencyclidine (PCP) revealed several advantages of the drug over more conventional anesthetics: pharyngeal and laryngeal reflexes were unchanged and there was minimal depression of the cardiovascular and respiratory systems [6]. However, the use of PCP as an anesthetic in humans was abandoned due to the frequent occurrence of emergence delirium, a state characterized by excitation, hallucinations, and irrational behavior during the recovery period. Similar emergence reactions limit the usefulness of ketamine, the only dissociative anesthetic currently available for use in humans. While PCP is no longer used clinically, the treatment of PCP intoxication in drug abusers is a common therapeutic challenge [13,14]. Thus, a drug capable of antagonizing certain effects of PCP might be useful as an adjunctive medication for improved dissociative anesthesia or as a treatment for PCP intoxication.

Tang and Franklin [16] recently suggested clonidine as a potential treatment for PCP intoxication. This was based on their observation that clonidine blocks the disruptive effects of PCP on a shock avoidance task in which rats are required to make a light-dark discrimination in a Y-maze. However, the efficacy of clonidine as a PCP antagonist seems not to apply to all behavioral variables. Clonidine does not block PCP-induced disruption of rotarod performance or PCP's anticonvulsant effects [18]. Tests of clonidine's ability to antagonize the discriminative stimulus properties of PCP in rats produced intermediate results; greater than 50% PCP-appropriate responding was observed with all doses of clonidine which were combined with the training dose of PCP [18].

It has previously been demonstrated that PCP disrupts the performance of rats in a radial maze [8,10]. Results of preliminary experiments indicate that ketamine affects rats in a similar manner (McCann and Winter, unpublished). The initial purpose of the present investigation was to evaluate the ability of clonidine to antagonize the effects of PCP and ketamine in a radial maze. In addition, the interactions of clonidine with PCP and ketamine were examined with respect to effects on righting reflex. Finally, in an effort to explain the resulting behavioral data, the effects of clonidine pretreatment on levels of PCP and PCP metabolites in rat brain were examined.

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METHOD

Animals

All subjects were male Fischer 344 rats obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA) at approximately four weeks of age. They were housed in pairs under a natural light-dark cycle and had free access to water in the home cage. Subjects were gradually reduced to 75–80% of their expected free-feeding weight and maintained at that level by limiting access to dry food to two hours per day.

Apparatus

The radial maze was similar in design to that which was described by Olton and Samuelson [11,12]. It consisted of a central hub, 34 cm in diameter, with eight 86 cm by 9 cm arms radiating from it. The aluminum walls of each arm were 10 cm high at the center of the maze and sloped to a height of 6 cm at the end of the arms. At the end of each arm and along the sides, extending 20 cm toward the center of the maze, pieces of clear Plexiglas increased the total height of the walls to 13 cm. The rest of the maze was constructed entirely of aluminum, with the exception of the food wells which were plastic cups 1.5 cm deep with a diameter of 2 cm. One food well was located at the end of each arm. The entire maze was elevated 46 cm from the floor.

Procedure

Training in the radial maze. At the beginning of each training session a subject was placed in the center of the maze with a 45 mg food pellet (P. J. Noyes Company, Lancaster, NH) located at the end of each arm. For the first session only, a pellet was also placed a short distance from the starting point to encourage exploration. Arm entries, defined as four paws within an arm, were scored by visual observation. The amount of time required to make the first eight arm entries was also recorded. A session lasted until all eight arms were entered or 10 minutes had elapsed. When a subject entered all eight arms during a session, then performance was analyzed in terms of efficiency. Efficiency was defined as the percentage of arm entries which were correct (not reentries) out of all arm entries made while completing the maze, i.e., 8/total number of arm entries, expressed as a percentage. Performance was also analyzed in terms of rate, defined as the number of arm entries made per minute during the first eight arm entries of a session. Each subject received training sessions three times a day, 1 to 2 hours apart, on Mondays and Thursdays or Tuesdays and Fridays (six sessions per week). Stable performance was assumed to be present when subjects reached a criterion of 89% efficiency in five consecutive sessions. Training was continued for a maximum of 30 sessions; subjects which did not reach criterion performance within this time were excluded from the experiments.

Ten subjects (Group I) which had participated in previous studies in the radial maze were used to evaluate the ability of clonidine pretreatment to prevent the disruptive effects of ketamine on performance in the maze. These subjects received no drug treatments for at least 3 months prior to the study. In addition, two groups of subjects were trained immediately prior to the present experiments. Group II (N=15) was used to evaluate the ability of clonidine pretreatment to prevent the disruptive effects of PCP on performance. Group III (N=15) was used to evaluate the ability of clonidine, administered 15 minutes after PCP, to reverse the effects of PCP.

Drug tests in the radial maze. After training, subjects performed in the maze two times a day on Mondays and Thursdays or Tuesdays and Fridays. No injections were given prior to the first session each day, a session identical in design to a training session. When a subject performed with at least 89% efficiency in its first session, a test session was given 1 to 2 hours later in which the effects of vehicle or drug injections were evaluated. When a subject performed with less than 89% efficiency in its first session, no injections were given prior to its second session. Test sessions lasted until all 8 arms were entered or for a maximum of 10 minutes. In addition to rate and efficiency, performance during test sessions was analyzed in terms of the number of entries made to previously visited arms (reentries) during the first 8 arm entries of a session. This additional measure of performance was needed when high doses of PCP prevented some subjects from completing the maze during a test session (no efficiency values could be calculated for these subjects).

Righting reflex tests. Following injections of PCP or ketamine, subjects were tested for the presence of a righting reflex every 5 minutes for 1 hour or until a righting reflex was regained. Righting reflex was considered absent when a subject failed to place all four paws in contact with a flat surface 3 seconds after being placed on its back. Data were expressed as the percentage of subjects anesthetized (righting reflex lost) and the mean duration of anesthesia.

Measurement of tritium levels in rat brain after administration of [^{3}H]PCP. Subjects received 40 μCi/kg of [^{3}H]PCP in a solution which also provided 4 mg/kg unlabeled PCP. Fifteen minutes after injections of [^{3}H]PCP, subjects were killed by decapitation. Brains were then immediately removed and dissected as described by Glowinski and Iversen [5]. However, no effort was made to separate the hypothalamus from the midbrain and the six resulting brain regions were cerebellum, cortex, hippocampus, medulla, midbrain/hypothalamus, and striatum. Each brain region was weighed and then dissolved by incubating at 55°C for 24 hours in 1 ml/100 mg protosol (NEN Research Products, Boston, MA). Radioactivity was measured in glass scintillation vials using a constant ratio of 15 ml scintillation fluid: 1 ml protosol: 100 mg tissue. Background radioactivity was determined by using brain tissue from a subject not injected with [^{3}H]PCP. Data representing total radioactivity minus background were expressed as disintegrations per minute (DPM)/100 mg tissue. Efficiency of counting ranged from 26 to 33%.

Drugs

Phencyclidine HCl was provided by the National Institute on Drug Abuse, Rockville, MD. Clonidine HCl was obtained from Boehringer Ingelheim Ltd., Ridgefield, CT. Both drugs were dissolved in saline. Ketamine HCl (Vetalar, Parke-Davis) was obtained as a 100 mg/ml solution and diluted with saline as needed. [Piperidyl-3,4-^{3}H(N)]phencyclidine (specific activity 47.6 Ci/mmol) was obtained from NEN Research Products, Boston, MA. All drugs were injected IP in a constant volume of 1 ml/kg of body weight.

Statistics

In behavioral experiments, clonidine treatments were counterbalanced with their corresponding control treatments

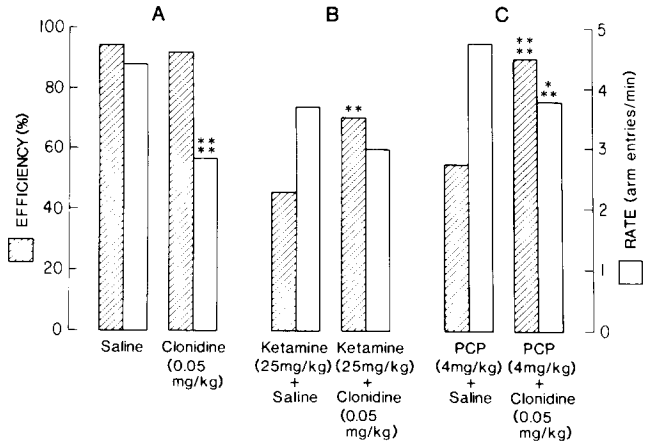

FIG. 1. Effects of clonidine (0.05 mg/kg) administered (A) alone (N=25), (B) prior to 25 mg/kg of ketamine (N=10), and (C) prior to 4 mg/kg of PCP (N=15) in an 8-arm radial maze. Clonidine, ketamine and PCP were injected IP 30, 5 and 15 min before testing, respectively. Each value represents the mean of 1 determination in each subject. Left scale: efficiency (hatched bars). Right scale: rate of responding (open bars). $^{**}p<0.01$; $^{***}p<0.005$; $^{****}p<0.001$.

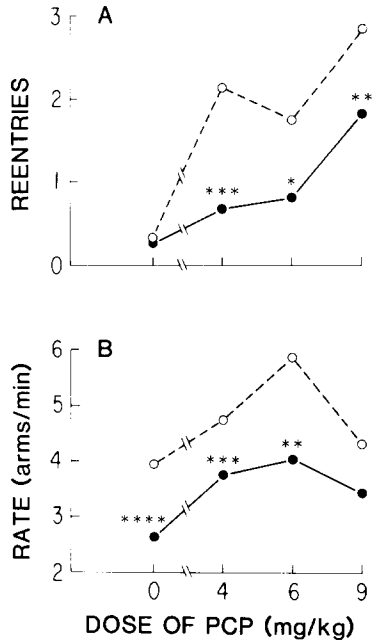

FIG. 2. A. and B. Dose response relationship for PCP alone (15 min before testing; open circles) and in combination with clonidine pretreatment (0.05 mg/kg, 30 min before testing; closed circles) in an 8-arm radial maze. Each point represents the mean of 1 determination in each of 15 subjects. Abscissa: dose of PCP expressed on a log scale. Ordinates: A—reentries during the first 8 arm entries of a session; B—rate of responding. $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.005$; $^{****}p<0.001$.

in a crossover design. Behavioral data corresponding to clonidine treatments were compared with control data by means of individual applications of the Wilcoxon signed ranks test for paired data. Where the use of an analysis of variance (ANOVA) is indicated, the Friedman two-way ANOVA by ranks was used. Concentrations of tritium in rat brain after clonidine and [^{3}H]PCP were compared with control data by means of individual applications of the t-test. Differences were considered to be significant if they would be expected to arise by random sampling alone with a probability less than 0.05.

RESULTS

All rats used in the radial maze experiments became highly efficient in obtaining the eight food pellets available during each training session. After 30 training sessions, two out of 42 subjects failed to reach a criterion of 89% efficiency in five consecutive sessions and were not included in the experimental groups. The mean number of sessions to achieve that criterion was 19 for Group I (N=10), 13 for Group II (N=15), and 16 for Group III (N=15).

Figure 1 shows the effects of 0.05 mg/kg of clonidine when administered by itself in Groups I and II (panel A), prior to ketamine in Group I (panel B), and prior to phencyclidine in Group II (panel C). All statistical comparisons were made between clonidine treatments and their corresponding controls in each panel. While efficiency (hatched bars, left scale) was not altered by clonidine alone, the decreases in efficiency caused by 4 mg/kg of phencyclidine and 25 mg/kg of ketamine were significantly attenuated by pretreatment with clonidine. Rate (open bars, right scale) was decreased by clonidine in each comparison. However, only the decreases observed when clonidine was administered by itself and prior to PCP were significant.

When the effects of clonidine pretreatment were evaluated with higher doses of PCP in Group II, the performance of some subjects became so disrupted that they failed to complete the maze within a 10 minute session. As a result, values for efficiency could not be determined for all subjects. However, all subjects made at least 8 arm entries during each session. Figure 2, panel A, shows the resulting data in terms of the number of entries made to previously visted arms (reentries) during the first 8 arm entries of each session. Values corresponding to 4 mg/kg of PCP represent a restatement of the data shown in Fig. 1, panel C. Effects of each dose of PCP on reentries (open circles) were significantly attenuated by pretreatment with 0.05 mg/kg of clonidine (closed circles). Figure 2, panel B, shows that clonidine significantly decreased rate when combined with all but the highest dose of PCP. In terms of reentries, an analysis of variance showed no significant difference between 4 saline test sessions given to the subjects during the course of the study. Rate during saline test sessions decreased significantly with time.

In Fig. 3 are seen the results of experiments in Group III designed to test the ability of clonidine to reverse the disruptive effects of 9 mg/kg of PCP. PCP was administered 45 minutes before test sessions and clonidine was administered 15 minutes after PCP. This is in contrast with the immediately preceding study in which PCP was administered 15 minutes before test sessions and clonidine was administered 15 minutes before PCP. Panel A shows that no significant reduction in the mean number of reentries was observed when 0.05 to 0.4 mg/kg of clonidine was administered after 9 mg/kg of PCP. In terms of both reentries and rate, analyses of variance showed no significant difference between 4 test

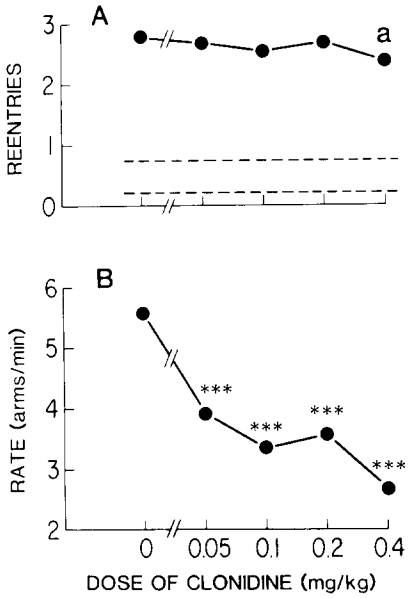

FIG. 3. A. and B. Dose response relationship for clonidine administered 15 min after PCP (9 mg/kg, 45 minutes before testing) in an 8-arm radial maze. Points corresponding to PCP in the absence of clonidine represent the means of 4 determinations in each of 15 subjects. All other points represent the means of 1 determination in each of at least 14 subjects. Hatched lines represent the range of means from 4 saline test sessions in all subjects. Abscissa: dose of clonidine expressed on a log scale. Ordinates: A—reentries during the first 8 arm entries of a session; B—rate of responding. [a]One of 15 subjects did not make 8 arm entries. ***$p<0.005$.

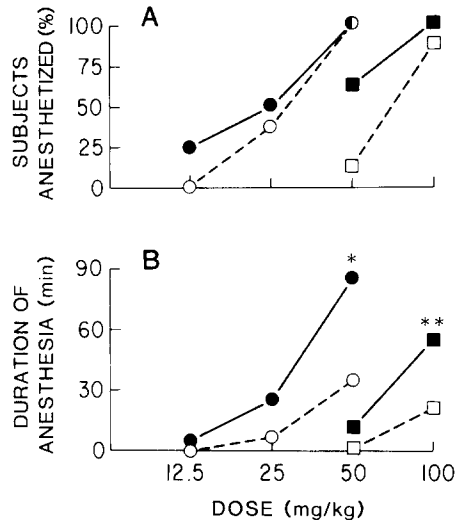

FIG. 4. A and B. Dose response relationships for PCP alone (open circles), PCP in combination with clonidine (0.05 mg/kg, 15 min before PCP; closed circles), ketamine alone (open squares) and ketamine in combination with clonidine (0.05 mg/kg, 15 min before ketamine; closed squares) in tests for righting reflex. Each point represents the mean of 1 determination in each of 8 subjects. Abscissa: dose of PCP or ketamine expressed on a log scale. Ordinates: A—percentage of subjects anesthetized; B—duration of anesthesia. *$p<0.05$; **$p<0.01$.

sessions in which subjects received 9 mg/kg of PCP in the absence of clonidine. Two horizontal hatched lines represent the range of means observed during 4 saline test sessions given during the course of the study. Rate (panel B) was significantly reduced by all doses of clonidine. When 0.4 mg/kg of clonidine was combined with 9 mg/kg of PCP, one subject failed to make 8 arm entries during a 10 minute test session; this subject exhibited a loss of righting reflex. Loss of righting reflex was never observed after 9 mg/kg of PCP in the absence of clonidine.

Figure 4 shows the results of studies designed to further test the ability of clonidine to increase the anesthetic effects of PCP and ketamine in 8 subjects from Group II. The dose-response relationships for PCP (open circles) and ketamine (open squares) on the percentage of subjects which lost their righting reflex (panel A) and the mean duration of this effect (panel B) were shifted to the left when 0.05 mg/kg of clonidine was administered as a pretreatment (solid circles and squares). The duration of anesthesia following 50 mg/kg of PCP and 100 mg/kg of ketamine was significantly increased by clonidine.

In Table 1 are the results of a study designed to evaluate the possibility of a pharmacokinetic interaction between clonidine and PCP. Two groups of three rats received 40 μCi/kg of [^{3}H]PCP in a solution which also provided 4 mg/kg of unlabeled PCP. Fifteen minutes prior to injections of [^{3}H]PCP one group received 0.05 mg/kg of clonidine and the other group received saline. Pretreatment with clonidine reduced concentrations of tritium by 42 to 55% in all brain areas 15 minutes after injections of [^{3}H]PCP. Concentrations of tritium in whole brain were reduced by 46%.

DISCUSSION

The present results do not support the suggestion by Tang and Franklin [16] that clonidine be used to treat the psychological disturbances in acute PCP intoxications. Although pretreatment of rats with clonidine was able to attenuate the disruptive effects of PCP on performance in a radial maze, clonidine was unable to reverse these effects when administered 15 minutes after PCP. In addition, the increased frequency and duration of anesthesia caused by PCP in the presence of clonidine suggest that clonidine could cause a loss of consciousness in PCP intoxicated patients.

The attenuation of PCP's effects in the maze after clonidine pretreatment is explicable by an alteration of the pharmacokinetics of PCP by clonidine. Lower concentrations of tritium measured in brain tissue when clonidine was administered prior to [^{3}H]PCP suggest decreased rates of absorption of PCP or decreased distribution of PCP and its metabolites to the brain. It is likely that a similar mechanism of interaction was responsible for the reported block of PCP's disruptive effects in a Y-maze [16], reductions in PCP-appropriate responding in drug discrimination tests [18], and attenuation of the increase in glucose metabolism caused by PCP in specific mouse brain areas [18]. In each of these studies PCP's effects were reduced when clonidine was administered at the same time as PCP. No attempts to reverse PCP's effects were reported. A similar effect of clonidine pretreatment on the pharmacokinetics of ketamine is likely to have caused the attenuation of ketamine's effects in the radial maze.

The increased frequency and duration of ketamine

TABLE 1

EFFECT OF CLONIDINE PRETREATMENT ON THE CONCENTRATION OF TRITIUM IN RAT BRAIN AFTER INJECTION OF [^{3}H]PCP

Brain Area	DPM/100 mg Tissue[a] Saline Control	Clonidine 0.05 mg/kg
Cerebellum	1247 ± 125	728 ± 81*
Cortex	1699 ± 169	883 ± 116†
Hippocampus	1330 ± 31	689 ± 135‡
Medulla	1228 ± 135	684 ± 105*
Midbrain/Hypothalamus	1427 ± 79	776 ± 88‡
Striatum	1483 ± 95	667 ± 57‡
Whole Brain	1464 ± 123	792 ± 100†

Saline or 0.05 mg/kg of clonidine was injected IP 15 min before 40 μCi/kg of [^{3}H]PCP. Subjects were killed 15 min after [^{3}H]PCP injections. [a]Means ± S.E.M., N=3 for each group. *$p<0.05$, †$p<0.01$, ‡$p<0.005$.

anesthesia observed after clonidine pretreatment in rats suggest that pretreatment of surgical patients with clonidine would allow lower doses of ketamine to be used. In addition, rats showed decreased muscle tone and did not vocalize during anesthesia when clonidine was administered prior to ketamine or PCP. These findings suggest that the quality of ketamine anesthesia may be improved by pretreatment of surgical patients with clonidine. Interestingly, in veterinary medicine xylazine is often used with ketamine to decrease the required anesthetic dose, decrease hyperactivity during the recovery period, improve muscular relaxation, and improve analgesia (e.g., [1, 17, 19]). Both xylazine and clonidine are agonists at alpha$_1$- and alpha$_2$-adrenergic receptors, with xylazine showing a higher selectivity for the alpha$_2$ subtype than clonidine [9]. Experience with xylazine in humans has come only through incidents of poisoning (e.g., [3,4]).

The ability of clonidine to reduce anesthetic requirements is not limited to dissociative anesthetics; requirements for halothane are also reduced by clonidine [2,7]. Interactions of clonidine with ketamine have not previously been reported. However, some surgical patients may have undergone ketamine anesthesia in the presence of clonidine; to avoid rebound hypertension, withdrawal of clonidine from patients receiving chronic antihypertensive therapy is not recommended prior to surgery [15]. Reports of such cases would be especially useful in determining the safety of the drug combination.

In summary, the present results illustrate the potential benefit of attempts to reverse, as well as prevent, the effects of PCP (or other drugs) when evaluating potential antagonists. The ability of clonidine pretreatment to attenuate effects of PCP in a radial maze appears to result from clonidine-induced decreases in the rate of absorption of PCP from its injection site or decreases in the fractional distribution of PCP and its metabolites to the brain. The failure of clonidine to reverse PCP's effects on efficiency in the maze and the greater frequency and duration of anesthesia observed after clonidine pretreatment should discourage attempts to treat PCP intoxication with clonidine. On the other hand, pretreatment of surgical patients with clonidine may allow lower doses of ketamine to be used and improve the quality of ketamine anesthesia.

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REFERENCES

1. Amend, J. F., P. A. Klavano and E. C. Stone. Premedication with xylazine to eliminate muscular hypertonicity in cats during ketamine anesthesia. *Vet Med Small Anim Clin* **67**: 1305–1307, 1972.
2. Bloor, B. C. and W. E. Flacke. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. *Anesth Analg* **61**: 741–745, 1982.
3. Carruthers, S. G., M. Nelson, H. R. Wexler and C. R. Stiller. Xylazine hydrochloride (Rompun) overdose in man. *Clin Toxicol* **15**: 281–285, 1979.
4. Gallanosa, A. G., D. A. Spyker, J. R. Shipe and D. L. Morris. Human xylazine overdose: a comparative review with clonidine, phenothiazines, and tricyclic antidepressants. *Clin Toxicol* **18**: 663–678, 1981.
5. Glowinski, J. and L. L. Iversen. Regional studies of catecholamines in the rat brain I: The disposition of ^{3}H-norepinephrine, ^{3}H-dopamine and ^{3}H-DOPA in various regions of the brain. *J Neurochem* **13**: 655–669, 1965.
6. Johnstone, M., V. Evans and S. Baigel. Sernyl (C1-395) in clinical anaesthesia. *Br J Anaesth* **31**: 433–439, 1959.
7. Kaukinen, S. and K. Pyykko. The potentiation of halothane anaesthesia by clonidine. *Acta Anaesthesiol Scand* **23**: 107–111, 1979.
8. Kesner, R. P., J. D. Hardy and J. M. Novak. Phencyclidine and behavior: II. Active avoidance learning and radial arm maze performance. *Pharmacol Biochem Behav* **18**: 351–356, 1983.
9. Kobinger, W. and L. Pichler. Alpha$_1$- and alpha$_2$-adrenoceptor subtypes: selectivity of various agonists and relative distribution of receptors as determined in rats. *Eur J Pharmacol* **73**: 313–321, 1981.
10. McCann, D. J. and J. C. Winter. Effects of phencyclidine, N-allyl-N-normetazocine (SKF-10,047), and verapamil on performance in a radial maze. *Pharmacol Biochem Behav* **24**: 187–191, 1986.
11. Olton, D. S. Spatial memory. *Sci Am* **236**: 82–93, 1977.
12. Olton, D. S. and R. J. Samuelson. Remembrance of places past: Spatial memory in rats. *J Exp Psychol [Anim Behav]* 2: 97–116, 1976.
13. Peterson, R. C. and R. C. Stillman. Phencyclidine: An overview. In: *PCP (Phencyclidine) Abuse: An Appraisal*, NIDA Research Monograph 21, edited by R. C. Peterson and R. C. Stillman. Rockville, MD: NIDA, 1978, pp. 1–17.
14. Smith, D. E. A clinical approach to the treatment of PCP abuse. In: *PCP (Phencyclidine): Historical and Current Perspectives*, edited by E. F. Domino. Ann Arbor, MI: NPP Books, 1981, pp. 471–485.

15. Stevens, J. E. Rebound hypertension during anesthesia. *Anaesthesia* **35:** 490–491, 1980.
16. Tang, A. H. and S. R. Franklin. Disruption of brightness discrimination in a shock avoidance task by phencyclidine and its antagonism in rats. *J Pharmacol Exp Ther* **225:** 503–508, 1983.
17. Van Pelt, L. F. Ketamine and xylazine for surgical anesthesia in rats. *J Am Vet Med Assoc* **171:** 842–844, 1977.
18. VonVoigtlander, P. F., A. H. Tang, M. C. Ochoa, S. R. Franklin and J. H. Triezenberg. A search for phencyclidine antagonists. In: *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*, edited by J. M. Kamenka, E. F. Domino and P. Geneste. Ann Arbor, MI: NPP Books, 1983, pp. 627–638.
19. White, G. L. and D. D. Holmes. A comparison of ketamine and the combination ketamine-xylazine for effective surgical anesthesia in the rabbit. *Lab Anim Sci* **26:** 804–806, 1976.