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THE CONVULSANT AND ANTICONVULSANT EFFECTS OF PHENCYCLIDINE (PCP) AND PCP ANALOGUES IN THE RAT

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The pro- and anticonvulsant effects of phencyclidine (1-[1-phenylcyclohexyl]piperidine HCl, PCP), a number of its analogues, and SKF 10047 were investigated in rats. The PCP analogues were compounds produced by substitutions for the phenyl and piperidine rings of PCP and were selected to elucidate the structure-activity relationships existing between PCP and its pro- and/or anticonvulsant effects. All of the compounds, except ketamine, induced convulsions at high (12.8–25.6 mg/kg, i.v.), yet almost always sublethal doses. Ketamine failed to induce convulsions, even at lethal doses (51.2 mg/kg, i.v.). The acute pro- or anticonvulsant actions of PCP were then investigated. Rats were subjected to transorbital electroconvulsive shock subsequent to i.p. injections of saline or 0.625, 2.5, 5.0, 10.0 or 20.0 mg/kg PCP. It was found that PCP induced an acute, dose-dependent anticonvulsant effect. The acute pro- and/or anticonvulsant actions of the remaining compounds were then investigated by administration of electroconvulsive shock subsequent to i.p. injections of saline or one of two doses of each compound. The low and high doses of each compound were selected to be behaviorally equivalent to 2.5 and 10.0 mg/kg PCP i.p., respectively. With one exception, each dose of each drug induced an acute anticonvulsant action, with no difference in efficacy between the compounds tested. However, PCA (produced by substitution of an amine for the piperidine ring of PCP) induced a statistically greater anticonvulsant action at the higher, compared to the lower, dose. In addition, PCA was the only compound to eliminate all motor signs of the electrically induced seizure. It was concluded that substitution of an amine group for the piperidine ring increased the efficacy of PCP's anticonvulsant action but that other substitutions for that ring or the phenyl ring had little influence on anticonvulsant efficacy.

INTRODUCTION

Phencyclidine (1-[1-phenylcyclohexyl]piperidine HCl, PCP) has a wide spectrum of pharmacological activity[11]. Despite the convulsant action of large doses of PCP, low doses have been shown to possess anticonvulsant actions against seizures induced by a variety of means in a number of species. In rats, PCP increased the latency to seizure subsequent to flurothyl administration[14], decreased the intensity of pentylenetetrazol- and strychnine-induced seizures[7,18], and increased kindled seizure thresholds[13]. In mice, the intensity of pentylenetetrazol, audiogenic or electrically induced seizures were reduced by prior administration of PCP[5,6,15,24]. Finally, PCP decreased the intensity of pentylenetetrazol convulsion in rabbits[18].

Ketamine (2-(o-chlorophenyl)-2-methylamino cyclohexanone HCl) is the only PCP analogue which is approved for clinical use. At large doses, it shares the anesthetic and convulsant actions of PCP[23]. At low doses it acts as an anticonvulsant in a number of species, including man[3,9,15,17,20,23]. However, even low doses of ketamine can induce seizures during or subsequent to chronic adminis-

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tration in the rat[16], when administered to either rats or cats with experimentally induced epileptogenic foci[1,10], and when given to certain epileptic humans[2,4,12].

The present study was conducted to determine the acute convulsant and anticonvulsant actions of PCP, various PCP analogues, ketamine and SKF 10047 on electrically induced seizures in rats. The various analogues were selected to determine the role of the piperidine ring and phenyl ring in the convulsant and/or anticonvulsant actions of PCP.

MATERIALS AND METHODS

Animals

Female Sprague–Dawley rats (Hilltop Lab Animals, Scottdale, PA) weighing between 180 and 230 g, were used. They were housed in groups of 3 in transparent plastic cages (21 cm wide by 32 cm long by 17 cm deep). However, when implanted with jugular catheters, the rats were housed singly. They were given food and water ad libitum and were maintained on a light-dark cycle of illumination from 06.00 to 22.00 h.

Drugs

All of the compounds used were obtained from the National Institute on Drug Abuse (Bethesda, MD), except for ketamine (Ketalar), which was obtained from Parke–Davis (Morris Plains, NJ). All compounds were dissolved in saline (or in the case of ketamine, diluted with saline) to 1 ml/kg for i.p. injections or to an injection volume of 0.1 ml/rat for i.v. injections. Fig. 1 provides the structures of the compounds used, which included PCP, ketamine, N-ethyl-1-phenylcyclohexylamine HCl (PCE), N-(s-butyl)-1-phenylcyclohexylamine HCl (NsBPCA), 1-phenylcyclohexylamine HCl (PCA), N-methyl-1-phenylcyclohexylamine HCl (NMPCA), 1-(1-phenylcyclohexyl)-pyrrolidine HCl (PCPY), 1-[1-(2-thienyl)cyclohexyl]piperidine HCl (TCP), 1-[1-(2-thienyl)-cyclohexyl]pyrrolidine HCl (TCPY), and N-allylnormetazocine HCl (SKF 10047). All drug injections were administered between 13.00 and 17.00 h.

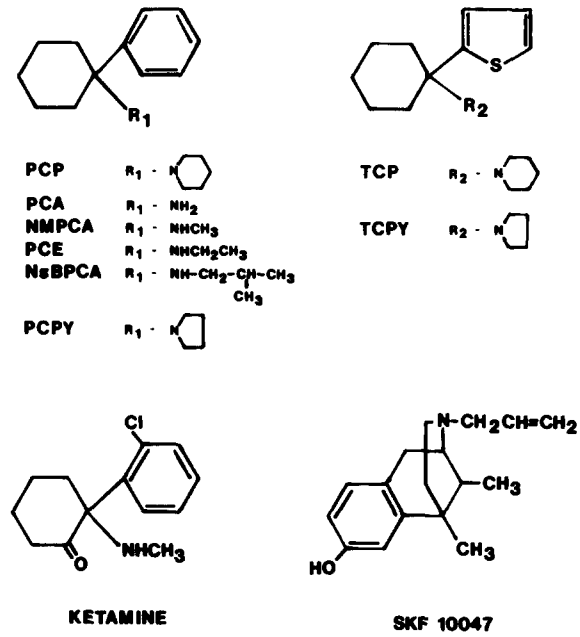

Fig. 1. Chemical structures of PCP, related analogues, and SKF 10047. The top left structure represents the phenylcyclohexyl structure with a piperidine ring, or a nitrogen having zero, one or two alkyl groups (R_1). The top right structure represents the thienylcyclohexyl structure with a piperidine or pyrrolidine ring (R_2). The bottom left structure represents ketamine while the bottom right structure represents SKF 10047. See the Introduction and Materials and Methods sections for the complete chemical names of all compounds tested.

Acute convulsant effects

Rats were anesthetized with 0.1 ml/50 gm body weight i.p. Chloropent (Fort Dodge Laboratories, Fort Dodge, IA). Anesthesia was maintained with methoxyflurane (Metofane, Pitman-Moore, Washington Crossing, NJ), as needed. Chronic Silastic (Dow Corning Corporation, Midland, MI) jugular catheters were implanted according to the method reported by Weeks and Davis[2]. Following a 3-day surgical recovery period, geometrically increasing cumulative i.v. doses of the 10 compounds were given at 30-min intervals over a range of 0.1–51.2 mg/kg. Six drug-naive rats were employed for each drug investigated. The ED_{50} for the induction of overt convulsions (myoclonic and/or tonic convulsions) by each drug was recorded.

Acute pro- and anticonvulsant effects of PCP

The pro- and anticonvulsant properties of PCP were studied by assessing its ability to increase or decrease, respectively, the intensity of electrically induced convulsions. Electroconvulsive shock was induced by a constant-current electroshock apparatus with foot pedal delivery (Wahlquist Instruments, Salt Lake City, UT). A 32 mA, 0.2-s transorbital shock was administered by placing the corneal electrodes over the eyes of restrained rats. A small amount of saline was placed on the rats' eyes immediately prior to application of the stimulus in order to increase conductivity. Rats were given only one shock and were released immediately after application of the stimulus. Two experimenters (one of whom was blind to the conditions of the experiment) used a 5-point scale to evaluate convulsion intensity as follows: 0, stunned only; 1, facial and vibrissae tremor; 2, clonic forepaw treading; 3, tonic forelimb extension; 4, tonic forelimb and hindlimb extension, and 5, death. The shock level employed was selected to induce a convulsion intensity of '3' in control rats. Thus, both increases and decreases in the intensity of the convulsion subsequent to drug treatment, indicating convulsant and anticonvulsant activity, respectively, could be observed.

Shocks were administered once every 48 h, 15 min after i.p. injection of saline or PCP. Baseline response to shock was determined after saline injection on Day 1. On Day 3, the effects of saline and 0.625, 2.5, 5.0, 10.0 and 20.0 mg/kg PCP on convulsant intensity were determined. On Day 5 the effect of saline on all the animals was again determined. Six drug-naive rats were used per dose tested. Rats given saline prior to each convulsion acted as controls for the repeated exposure to shock over the 5 days of the experiment. In order to control for individual variability in response to the electrical stimulus, the data were transformed into a difference score for each animal by subtracting the convulsant intensity rating obtained on Day 1 from that obtained for the same rat on Day 3 and 5. Thus, assuming a magnitude sufficiently great to enable achievement of statistical significance when compared to saline difference scores, a positive difference score for drug-treated rats on Day 3 indicated an acute proconvulsant effect, a negative value revealed an acute anticonvulsant action, and a value of zero indicated no effect. Similarly, difference scores obtained on Day 5 revealed whether the acute drug treatment on Day 3 retained any residual effect on Day 5, or induced an effect in opposition to that seen at Day 3 (that is, a rebound phenomenon). The Kruskal–Wallis and Mann–Whitney tests were used to compare the difference scores obtained for saline- vs PCP-treated animals.

Acute pro- and anticonvulsant effects of PCP Analogues. The effects of the 9 remaining compounds on electrically induced convulsions were investigated in a manner identical to that described above. Behaviorally equivalent doses of the compounds were selected to assure that between-drug differences in pro- and anticonvulsant potencies were more likely the result of differential effects on electrically induced convulsions than the result of non-specific drug effects. In previous experiments designed to assess the overt behavioral and electrophysiological effects of the compounds (manuscript in preparation), rats had been given cumulative i.v. doses of each of the compounds, including PCP, 15 min prior to placement upon a rotarod apparatus. Rather than conducting a full dose-response curve for each of the remaining 9 compounds, in the present experiment each compound was evaluated at an i.p. dose equivalent to the i.v. dose that caused rotarod failure and an i.p. dose equivalent to one quarter of the i.v. rotarod failure dose. Thus, the amount of ataxia experienced at either dose was limited to a level less than or equal to that occurring at rotarod failure. The rotarod failure experiment was also used to derive i.p. doses of PCP. Naive rats were employed to redetermine the effects of these derived doses of PCP on electrically induced convulsions. Assurance of behavioral equivalence of all derived doses with the derived PCP doses was obtained by using the rating scale of Sturgeon et al.[19] and a videotaped record of the experiment to evaluate the degree of locomotor activity, stereotypy and ataxia induced at 14-min postinjection (1 min preshock). A third

observer, blind to both drug-treatment and dose, performed these behavioral observations.

Six drug-naive rats were used at each dose of each drug. Due to the large number of animals involved, the drugs were investigated in groups of 3, each group with its own saline-treated control. Kruskal–Wallis and Mann–Whitney tests were used for statistical analysis.

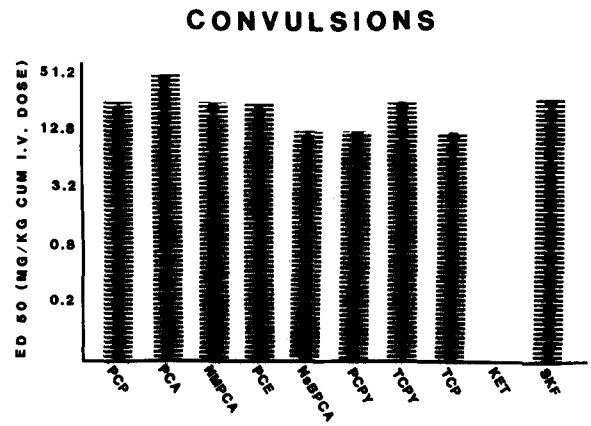

Fig. 2. ED_{50} values for induction of convulsions by PCP, related analogues and SKF 10047. All compounds were administered by cumulative i.v. injections. KET = ketamine, SKF = SKF 10047.

RESULTS

Acute convulsant effects

Fig. 2 reveals the ED_{50} of each drug for induction of overt convulsions in the rat. Nine of the 10 compounds induced convulsions at doses ranging from 12.8 to 51.2 mg/kg. However, ketamine did not cause convulsions in any of the 6 animals even though, as with the other compounds, dosing continued until death occurred.

Acute pro- and anticonvulsant effects of PCP

Table I lists the mean difference scores obtained on Days 3 and 5 for rats given saline or 0.625, 2.5, 5.0, 10.0 or 20 mg/kg PCP 15 min prior to the electrical stimulus on Day 3. A Friedman's two-way ANOVA revealed that there was no effect on saline-treated rats of the multiple exposure to the electrical stimulus. A Kruskal–Wallis test revealed that the PCP treatments induced a significant decrease in Day 3 convulsant intensities ($H = 10.22, P < 0.05$), but had no effect on Day 5 convulsion intensities. Mann–Whitney tests showed that each of the doses induced a statistically significant decrease in Day 3 convulsion intensity. Inspection of the Day 3 mean difference scores suggests that the reduction in convulsion intensity was dose-dependent, although statistical significance of between dose differences were not achieved.

TABLE I

The effect of PCP on electrically induced convulsions

A mean difference score of zero indicates no change. When statistically significant, a negative score denotes anticonvulsant action and a positive score denotes a proconvulsant action of the drug; n, 6; * $P < 0.05$; ** $P < 0.01$.

	PCP dose (mg/kg, i.p.)					
	0	*0.625*	*2.5*	*5.0*	*10.0*	*20.0*
DAY 3 MINUS DAY 1						
Mean Difference Score	0.33	− 0.83*	− 1.00*	− 1.00*	− 1.33**	− 1.67**
DAY 5 MINUS DAY 1						
Mean Difference Score	0.33	− 0.67	0	− 0.33	0.17	− 0.50

Acute pro- and anticonvulsant effects of PCP analogues

Table II lists the mean difference scores obtained on Days 3 and 5 for each dose of PCP and the analogues. A Friedman's two-way ANOVA revealed that there was no effect of the multiple exposure to the electrical stimulus on saline-treated rats. A Kruskal–Wallis test revealed that there were no differences in convulsion intensity between the various saline-treated control groups. Thus, the control groups were pooled for further statistical analysis. For all 10 compounds, including PCP, both doses of each drug induced a statistically significant decrease in convulsant intensity on Day 3 and had no effect on convulsant intensity on Day 5. In most cases, perhaps because only two doses of each compound were studied, there was no significant difference in anticonvulsant efficacy between the low and high doses of each drug. However, PCA did demonstrate a statistically greater anticonvulsant action at the higher, compared to the lower, dose of the drug ($U = 6, P < 0.05$). In addition, the high dose of PCA was the only dose of any of the compounds to completely eliminate all motor signs of the convulsions, thereby reducing convulsant intensity rating scores to '0'.

TABLE II

The effect of PCP and PCP-analogues on electrically induced convulsions

A mean difference score of zero indicates no change. When statistically significant, a negative score denotes anticonvulsant action and a positive score denotes a proconvulsant action of the drug; n = 6; * $P < 0.05$; ** $P < 0.01$.

Drug	*Dose (mg/kg ip)*	*Mean difference score*	
		Day 1–3	*Day 1–5*
SALINE	–	0.42	0.13
PCP	2.5	−0.83*	0.17
	10.0	−0.92**	0.17
PCA	10.0	−0.75*	0.00
	40.0	−2.58**	0.17
NMPCA	5.0	−0.83*	0.50
	20.0	−1.40*	0.33
PCE	1.25	−0.66*	0.83
	5.0	−0.75*	0.17
NsBPCA	2.5	−0.75*	0.33
	10.0	−0.83*	−0.33
PCPY	1.25	−0.75*	−0.17
	5.0	−0.83*	0.00
TCP	0.625	−0.33*	0.17
	2.5	−0.33*	0.33
TCPY	1.25	−0.33*	0.50
	5.0	−0.83*	0.50
KET	5.0	−0.50*	0.00
	20.0	−0.50*	0.83
SKF	5.0	−0.50*	−0.17
	20.0	−0.50*	−0.33

DISCUSSION

The results of the above experiments reveal that PCP, its analogues, and SKF 10047 each induce convulsions at high, yet sublethal, i.v. doses. The sole exception to the above conclusion is ketamine, which did not cause convulsions when administered in a cumulative i.v. dosing schedule to the point of lethality. However, it should be noted that ketamine has been shown by others to induce seizures in susceptible humans[2,4,12], in rats and cats with experimentally induced epileptogenic foci[1,10], and during and subsequent to chronic administration in the rat[16]. The results of these 3 studies suggest that ketamine does possess proconvulsant activity. However, it appears that ketamine, unlike the other compounds in the present experiments, requires that rats possess a pre-existing susceptibility to convulsions before this proconvulsant action can be observed.

PCP exhibited an acute anticonvulsant action over a wide range of doses, from those which were otherwise behaviorally inactive to those which induced tremor and forepaw treading. It should be remembered that the design of the study enabled determination of whether the drug was exerting a proconvulsant action, indicated by an elevation of acute convulsant intensity scores, or an anticonvulsant action, indicated by a decrease in acute convulsant intensity scores. While saline-treated rats demonstrated a slight, but statistically insignificant, increase in convulsant intensity from Day 1 to Day 3, none of the 30 rats given PCP

revealed any increase in convulsant intensity. Instead, these drug-treated rats most frequently revealed a decrease in convulsant intensity, while some rats revealed no change in convulsant intensity. While most of the drug-treated rats displayed convulsions that were assigned a rating of '2' (clonic forepaw treading), there was a dose-dependent tendency towards convulsions rated as '1' (facial and vibrissae tremor). However, even the highest dose (20 mg/kg) of PCP did not reduce convulsions to a rating of '0' (stun only) in any of the rats tested.

While each dose of PCP exhibited acute anticonvulsant action, none had any statistically significant effects on the intensity of convulsions on Day 5, 48 h after drug treatment. This suggests that neither PCP nor its metabolites induce anticonvulsant action over extended periods of time subsequent to a single acute administration. In addition, there does not appear to be any compensatory response ('rebound') to the acute anticonvulsant action of PCP. Preliminary studies indicate that even after 14 days of twice daily i.p. injections of 5 mg/kg PCP there is no evidence of tolerance to the anticonvulsant action nor a 'rebound' phenomenon subsequent to a halt in the drug administration. This preliminary finding with PCP contrasts sharply with the finding of others that ketamine induces convulsions both during long-term administration and subsequent to cessation of drug administration[16].

PCP, each of the PCP analogues, and SKF 10047 all induced an acute anticonvulsant effect, indicated by a negative value for the difference scores obtained from Day 1 minus Day 3. None of the drugs exerted an acute proconvulsant action. In addition, none of the compounds exerted a statistically significant pro- or anticonvulsant action on Day 5. While PCA, the compound created by substitution of an amine for the piperidine ring, was the only analogue which induced a statistically greater anticonvulsant action at the higher dose than at the lower dose, the failure to obtain a dose-response effect for the remaining compounds most likely was the result of the limited number of doses investigated for each compound. However, PCA did induce a greater anticonvulsant action than did any of the other compounds tested, despite the equivalence of all the low and high doses of the compounds in capacity to induce locomotion, stereotypy and ataxia. In addition, PCA was unique in that it was the only compound to reduce convulsant intensity to '0' (stun only). In fact, convulsant intensity subsequent to PCA treatment was reduced to '0' in all of the high dose animals and in one of the low dose animals. Finally, although all the other compounds, except ketamine, induced convulsions at an i.v. dose below that which induced lethality, PCA was again unique in that it failed to induce convulsions until a lethal i.v. dose was administered.

Others have determined that the structural alterations of PCP characteristic of the analogues tested in the present study result in differences in potency, rather than qualitative differences in activity[8,21]. The present experiments investigated the effects of derived i.p. doses that were selected as equipotent in terms of the effects of the original i.v. doses on rotarod performance and verified as equipotent in induction of locomotion, stereotypy and ataxia. This strengthens the hypothesis that the profound and unique anticonvulsant action of PCA arises from the structural differences between it and the other compounds rather than from mere differences in capacity to induce non-specific drug actions. The lack of any difference in anticonvulsant properties resulting from alkyl group substitutions (methyl, ethyl, isobutyl), or the existence of a pyrrolidino rather than piperidine ring, provides additional evidence of the importance of the amine group of PCA to its increased anticonvulsant action. Finally, an increased therapeutic index ratio is conferred on the PCP and PCPY molecules by thienyl ring substitution for the phenyl ring[21]. Yet, no differences were observed in the present study in the anticonvulsant action of PCP or PCPY compared to TCP and TCPY, respectively. Thus, substitution of the phenyl ring of PCA by a thienyl ring (TCA, 1-[1-(2-thienyl)cyclohexyl]amine) might result in a molecule both efficacious and relatively safe. Since the anticonvulsant actions of all of the PCP-related molecules, including PCA, occurred at doses that were one quarter of those that induced rotarod failure, and since the anticonvul-

sant action of PCP occurred at a dose devoid of observable behavioral effects (0.625 mg/kg), the anticonvulsant action of compounds such as TCA may be effective at doses that are otherwise behaviorally inactive.

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