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Short communication

PHENCYCLIDINE-INDUCED CATALEPSY IN PIGEONS: SPECIFICITY AND STEREOSELECTIVITY

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A procedure is described for the rapid assessment of cataleptic activity (loss of righting, without head-drop and without eye closure) of phencyclidine-type drugs. Single- and cumulative-dosing procedures with phencyclidine and ketamine produced similar results. Pentobarbital produced loss of righting at doses which also induced head-drop and eye closure. Catalepsy was induced exclusively by the d-isomers of ketamine, 1-(1-phenylcyclohexyl)-3-methylpiperidine and α-dioxadrol. The procedure is suitable for studying compounds which may interact with phencyclidine receptors.

Cumulative dosing procedure Phencyclidine Catalepsy Pigeons

1. Introduction

The cataleptic effect of PCP in pigeons (characterized by a loss of the righting reflex without "head-drop", shown by an outstretched head and a ventrally flexed neck while the pigeon is laid on its back) is a simple test which may be pharmacologically specific in that various other CNS-depressant drugs appear to produce loss of righting, but only in combination with head-drop (Chen, 1965). The test has been used in the characterization of benz(f)isoquinoline derivatives (Zimmerman et al., 1983). The first aim of the present study was to investigate drug-induced catalepsy in pigeons using a procedure which allows the assessment of the entire dose-response curve during a single experimental session (e.g. Wenger, 1980), and to compare these results to data obtained when a single drug dose is evaluated per session. Second, the pharmacological specificity of PCP-induced catalepsy was investigated further by comparing in detail the cataleptic effects of PCP-like drugs with the effects of pentobarbital. Third, the stereospecificity of the catalepsy test in pigeons was explored by investigating several pairs of stereoisomers for their relative ability to induce catalepsy.

2. Materials and methods

2.1. Subjects

The subjects were nine experimentally naive White Carneaux pigeons (weighing between 450-550 g) which were housed in individual cages with water, grit, mixed grain and Purina pigeon checkers freely available.

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2.2. Procedure

The procedure was adapted from the procedure described by Chen (1965). A pigeon is held with the wings to the body and is laid on its back, while avoiding contact with its feet. Catalepsy was defined as the simultaneous occurrrence of 1) loss of the righting reflex, as evidenced by a failure of the pigeon to right itself within 15 s, 2) absence of head-drop (head-drop was defined as the head lying sideways and motionless on the observation surface during the entire 15 s test period, and 3) absence of eye closure. Handling of the pigeons and scoring were performed blind to the drug treatment.

In the cumulative-dose procedure, injections were given i.m. (inj. vol. 1 ml/kg) at 20 min intervals, and effects were tested 15 min after each injection. The dose of drug injected before each test was calculated to increase the total amount injected during the session by 1/4 log-unit steps. Cumulative dosing continued until a dose was reached at which all subjects showed catalepsy, or a limitation of further testing was imposed (e.g. solubility of drug). In the single dose procedure doses were administered per session which were equivalent to the total amounts injected in each of the several tests of the cumulative procedure. The time course of the drug effect was studied in both procedures by tests at 30, 60, 120, and 240 min after the last injection of the session. Cumulative-dosing sessions were separated by at least 48 h intervals. Single-dose sessions were separated by 24 h intervals.

Five pigeons were submitted to both cumulative- and single-dosing tests of PCP and its congener ketamine, and four of these pigeons were submitted to comulative-dosing tests of the isomers of 1-(1-phenylcyclohexyl)-3-methylpiperidine (PCMP), ketamine and α-dioxadrol. Four pigeons were used to study the effects of pentobarbital in a cumulative-dosing procedure.

2.3. Analysis

For each drug and each subject the lowest dose which produced catalepsy (referred to as the threshold dose) and the longest time interval at which catalepsy was still present (referred to as the threshold time) were determined. The results of the cumulative- and single-dosing tests of PCP and ketamine were analyzed by means of two-factor ANOVA with repeated measures on both factors (drug, procedure) (Keppel, 1973), for log threshold dose and log threshold time data separately. Differences in mean log threshold dose and mean log threshold time between catalepsy-inducing drugs were analyzed by means of one-factor repeated measures ANOVA.

2.4. Drugs

The drugs used were phencyclidine (PCP), (+)- and (−)-(PCMP) hydrochlorides (K.C.R. and T.R.B., National Institutes of Health), (±)-, (+)- and (−)-ketamine hydrochlorides (Warner-Lambert/Parke, Davis and Co., Ann Arbor, MI), dexoxadrol ((+)-α-dioxadrol) and levoxadrol ((−)-α-dioxadrol) hydrochlorides (Upjohn Laboratories, Kalamazoo, MI; A.E.J. and P.N.H., National Institutes of Health), and pentobarbital sodium. PCP was dissolved in sterile water to which a small amount of lactic acid was added. All other drugs were dissolved in 0.9% NaCl. Doses of drugs are expressed in the forms described above.

3. Results

Dose-response and time-response curves of ketamine and PCP are shown in fig. 1. Analysis of the threshold dose data, obtained with ketamine and PCP, showed a significant drug effect ($F(1,4) = 174.75$, $P < 0.001$). Neither the main effect of procedure nor the interaction effect was significant ($F(1, 4) = 1.47$, $F(1, 4) < 1.0$, respectively). Overall mean threshold doses (±1 S.E.M.) of ketamine and PCP were 14 ± 1.8 mg/kg and 1.5 ± 0.3 mg/kg respectively. Analysis of the threshold time data showed a significant drug effect ($F(1, 4) = 16.0$, $P < 0.025$). Other effects were not significant ($F < 1.0$). Overall mean threshold times were 33.4 ± 4.1 min (ketamine) and 43.7 ± 4.8 min (PCP).

The results obtained with pentobarbital (fig. 1) indicate that there is no dose level at which all subjects show a loss of righting without the con-

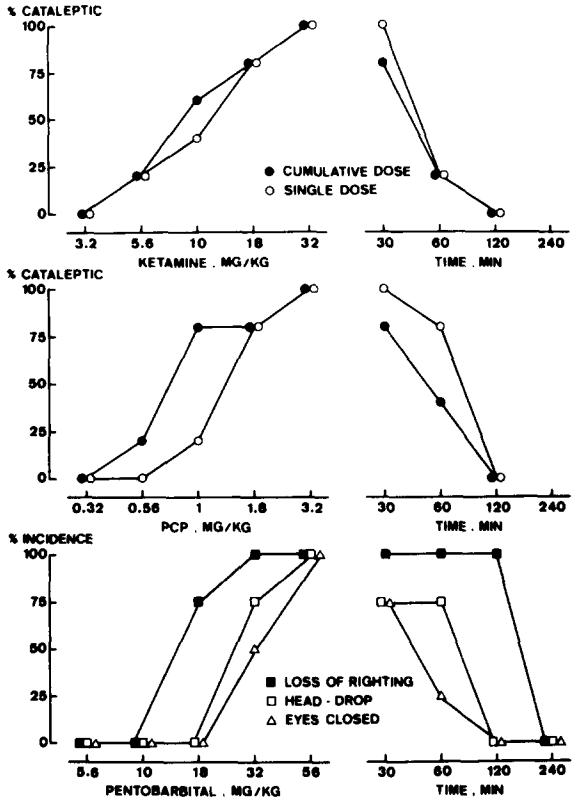

Fig. 1. Dose-effect and time-effect curves of ketamine-induced (upper panel) and PCP-induced (middle panel) catalepsy (loss of righting without head-drop and without eye closure) in pigeons (n = 5). Ordinates: percentage of subjects showing catalepsy. Abscissae: dose administered (left panels) and time after the injection of the largest dose administered. The time-effect curves were determined after all subjects had received the total dose specified in the figure. Lower panel: dose-effect and time-effect curves of pentobarbital in pigeons (n = 4). Ordinate: percentage of subjects showing loss of righting, head-drop, eye closure. Abscissae: cumulative dose administered, and time after the injection of the largest dose administered.

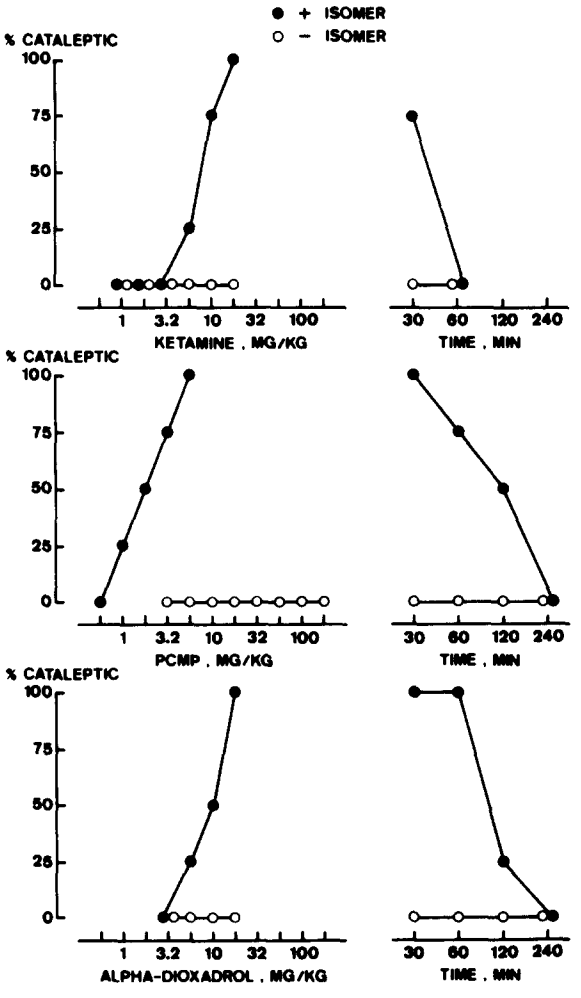

Fig. 2. Dose-effect and time-effect curves of catalepsy induced in pigeons (n = 4) by isomers of ketamine, PCMP and α-dioxadrol. Ordinates: percentage of subjects showing catalepsy. Abscissae: cumulative dose administered and time after the injection of the largest dose administered.

comitant occurence of head-drop and eye closure. Therefore, pentobarbital does not produce catalepsy as defined herein.

Catalepsy was induced exclusively by the (+)-isomers of ketamine, PCMP and α-dioxadrol (fig. 2). Increasing doses of levoxadrol were tested until the solubility limit was reached. Unlike the catalepsy induced by ketamine and PCP the highest dose of (−)-PCMP produced a loss of righting in combination with wing flapping and vocalization. One pigeon died after the administration of this dose. The drugs which induced catalepsy differed significantly in potency ($F(4, 12) = 17.05$, $P < 0.001$) and in duration of action ($F(4, 12) = 10.04$, $P < 0.001$). The mean threshold doses of PCP and of (+)-PCMP were significantly lower than the mean threshold doses of the other drugs tested ($P < 0.01$, Newman-Keuls procedure), and the mean threshold times of (+)-PCMP and dexoxadrol were significantly longer than the mean

threshold times of the other drugs ($P < 0.05$). All other differences were not statistically significant.

4. Discussion

The cumulative-dosing procedure produced results which are similar to results obtained in a single-dose procedure. Therefore, the cumulative-dosing procedure appears to be useful for the rapid assessment of drug-induced catalepsy in pigeons.

The finding that pentobarbital did not produce catalepsy is in agreement with and extends results reported by Chen (1965) and constitutes further evidence of the pharmacological specificity of the catalepsy test.

Stereoselectivity is an important criterion for receptor-mediated actions of drugs. Catalepsy was induced by the (+)-isomers of the drugs tested, but not by the (−)-isomers. These results confirm and extend previous observations on the stereoselective PCP-like behavioral (e.g. Herling et al., 1983) and biochemical (e.g. Hampton et al., 1982) effects of these isomers.

Phencyclidine can function as a discriminative stimulus in pigeons; a strong association between the potency of agents to induce catalepsy and the potency to induce PCP-like discriminative effects in pigeons has been established (Leander et al., submitted).

Acknowledgements

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