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Facilitatory Effect of Ketamine on Punished Behavior[1]

M. L. BRANDÃO,[2] J. C. S. FONTES AND F. G. GRAEFF

Department of Pharmacology, School of Medicine and Laboratory of Psychobiology, School of Philosophy, Science and Letters, 14.100 Ribeirão Preto, S.P., Brazil

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BRANDÃO, M. L., J. C. S. FONTES AND F. G. GRAEFF. *Facilitatory effect of ketamine on punished behavior.* PHARMAC. BIOCHEM. BEHAV. 13(1) 1–4, 1980.—In order to compare the effect of ketamine on punished and unpunished operant responding with that of pentobarbital and amphetamine, pigeons were trained to perform under a multiple fixed-interval 5 min, fixed-interval 5 min (shock) schedule of food presentation. In both schedule components, the first response after 5 min produced access to grain (FI5). In the punished component every response was followed by electric shock delivery. Lower effective doses of ketamine (1.7–5.6 mg/kg) caused moderate increases in punished FI responding with little or no alteration of unpunished response rates. Higher doses (10 and 17 mg/kg) decreased both punished and unpunished FI rates. Large increases in punished responding were caused by 10 mg/kg of pentobarbital. This and lower doses of the latter drug also moderately increased non-punished FI responding. The highest dose of pentobarbital used (17 mg/kg) decreased unpunished FI response rates while still increasing punished FI rates. Amphetamine caused dose-dependent decreases in punished responding at doses (0.17–1.0 mg/kg) that did not affect unpunished responding. Higher doses (1.7 and 3.0 mg/kg) of amphetamine also decreased unpunished FI rates, but to a lesser extent than punished response rates. From these and other reported results it may be concluded that ketamine affects schedule controlled behavior in characteristic ways, different from both minor tranquilizers and amphetamine-like drugs.

Pigeons Fixed-interval Punishment Ketamine Amphetamine Pentobarbital

KETAMINE as well as the closely related compound, phencyclidine are central nervous system stimulant drugs, which cause a characteristic sequence of behavioral changes. Lower effective doses enhance motor activity whereas higher doses induce ataxia, bizarre behavior and an immobile, cataleptic-anesthetic state, under which surgery can be performed. Still higher doses cause mioclonic or generalized seizures. In man, acute psychotic reactions with prominent hallucinatory phenomena are observed during emergence from anesthesia. In addition, cases of phencyclidine and, to a smaller extent, ketamine abuse have been reported [27].

Certain behavioral effects of subanesthetic doses of ketamine and phencyclidine in experimental animals are similar to those of amphetamine. Both drugs increase locomotor activity of mice and rats [5,6], and this effect is potentiated by the monoaminoxidase inhibitor, iproniazid [4].

It has also been shown that phencyclidine and ketamine have amphetamine-like effects on schedule-controlled behavior in pigeons [25] and in mice [26]. Lower doses of the drugs increased and higher doses decreased response rates during the fixed-interval component of a multiple fixed-interval, fixed-ratio (mult FI FR) schedule of food presentation in both species, whereas only dose-dependent rate decreases were observed in the FR component. These effects are characteristic of amphetamine-like drugs, as shown by these [25,26] and other reported studies [8, 16, 17, 21, 23]. In contrast, lower doses of pentobarbital increase FR as well as FI response rates while higher doses of the drug decrease FI responding to a larger extent than FR rates [7, 15, 21].

Nevertheless, preliminary reports [3,24] indicate that ketamine or phencylcidine facilitate behavior suppressed by punishment, whereas amphetamine usually does not increase punished responding [11, 13, 18]. On the other hand, marked facilitatory effects on punished responding are caused by barbiturates and other minor tranquilizers [11, 12, 14, 18, 19, 20, 22].

In the present study, the effect of ketamine on punished and unpunished responding of pigeons was compared to that of amphetamine and pentobarbital. A multiple schedule in which responding was maintained by food presentation at fixed intervals of 5 min (FI 5) in both schedule components, but was suppressed in one component by the delivery of response-contingent electric shock was used. This schedule has been shown to distinguish between different classes of behavior-acting drugs [18,20].

The present results show that ketamine released responding suppressed by punishment, but the magnitude of the ketamine effect was smaller than that of pentobarbital. In contrast, amphetamine caused only dose-dependent decreases in punished responding. These as well as the results

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reported by Wenger [25,26] indicate that ketamine affects operant behavior differently from both minor tranquilizers and amphetamine-like drugs.

METHOD

Animals

Four experimentally naïve, adult, male domestic pigeons were used. The subjects came from uncontrolled derivations of the species *Columba livia*. The birds were housed individually and maintained at a body weight of about 80% of the normal weight when given free access to food.

The experimental chamber consisted of a standard, two-key pigeon chamber (Grason-Stadler). The translucent response-key in the front panel, near the door could be transilluminated by a red or a green light (2 W); the remaining key was dark and inoperative throughout the experiments. A minimum force of a 15 gf was required to operate the response-key. Each effective response produced auditory feed-back by operating a relay. No other light was on during the experiments. A rectangular opening in the wall, near the floor gave occasional access to the feeder. A reinforcement consisted of 4 sec access to grain. During reinforcement the key-lights were off and the feeder was illuminated by a different light. The experimental chamber was placed inside a sound attenuated chest provided with a fan. Temperature inside the experimental chamber varied between 22 and 23°C.

The pigeons had nickel-chrome electrodes permanently implanted around the pubis bones. The electrodes were attached to a permanent leather harness [1]. During the experimental session, a plug was connected to a swivel, mounted on the top wall of the experimental chamber, by means of a flexible electric wire, allowing the bird to move around inside the box. Electric shocks were generated by a model 700 Grason-Stadler shock generator. Additional standard electromechanical equipment was employed for automatic programming and recording.

Procedure

A multiple fixed-interval 5-min, fixed-interval 5-min schedule of food presentation in which every response was punished with electric shocks in one component, but not in the other [18], was used. In both components of the mult FI5 FI5 (shock) schedule the first response after 5 min in the presence of an illuminated key was reinforced. If no response occurred within 1 min, the next schedule component was introduced without food delivery. In the punished component, every response was immediately followed by a 50 msec electric shock, except for the response which produced food. A red key-light signalled the punished component, whereas a green key-light was on during the unpunished component. The key-lights went off for 1 min between successive schedule components. During this period, responses had no programmed consequences. The punished and unpunished components alternated throughout the experimental session. The session always initiated with an unpunished component and terminated after nine presentations of each schedule component (approximately 110 min). The shock intensity was gradually increased and adjusted for each bird during several experimental sessions until punished responses were markedly reduced (about 5 to 30% of the number of unpunished responses), but not altogether abolished. The shock intensities used were 1.6 mA (pigeons P8 and P10), 2.0 mA (P6) and 3.0 mA (P11), 350 V r.m.s., AC.

TABLE 1

CONTROL RESPONSE RATES IN THE MULT FI5 FI5 (SHOCK) SCHEDULE OF FOOD PRESENTATION

Pigeon	Schedule component		Number of Sessions
	Unpunished FI	Punished FI	
	Responses per min (mean ± SD)		
P6	30.10 ± 10.39	2.97 ± 0.90	24
P8	21.12 ± 5.33	2.55 ± 0.60	8
P10	30.45 ± 9.20	8.57 ± 1.41	24
P11	38.97 ± 6.38	2.19 ± 0.74	24

The experiments were conducted daily from Monday through Friday. Drug or saline injection were given on Tuesday and Fridays. Thursdays were used as non-injection control sessions.

Analysis of Results

Responses were cumulatively recorded and the tracings were analyzed for shifts in response rates and patterns of responding. Average rates of responding were computed during each component of the multiple schedule from data recorded on digital counters. Each dose of the drugs was studied in two sessions per pigeon. In order to summarize dose-effect relationships, the mean rates of responding for each animal in two sessions at a given dose were converted to a percentage of the mean rate in control sessions; from these individual means a group mean and its standard error were calculated.

Due to illness, pigeon P8 was not used for the determination of the dose-response curves of amphetamine and pentobarbital.

Drugs

Sodium pentobarbital (Nembutal®, Abbott) *d,l*,amphetamine hydrochloride (Sigma) and ketamine hydrochloride (Ketalar®, Parke-Davis) were used. The drugs were dissolved in saline solution and injected into the breast muscle in a volume of 1 ml/kg, immediately before the experimental session. Doses of the drugs refer to salts. The ketamine dose-response curve was the first to be determined, followed by pentobarbital and amphetamine. For each drug, the different doses were injected in nonsystematic order. Each dose-response curve was preceded by five control sessions, at least, without any injection.

RESULTS

Control Performance under the Mult FI5 FI5 (shock) Schedule

The pattern of responding in both schedule components was typical of fixed interval performance [10] with an initial pause of variable duration at the beginning of each interval followed by rapidly accelerated responding up to a final rate that was sustained until reinforcement. However, the initial pause was longer and the final response rate considerably lower in the punished than in the unpunished component. As

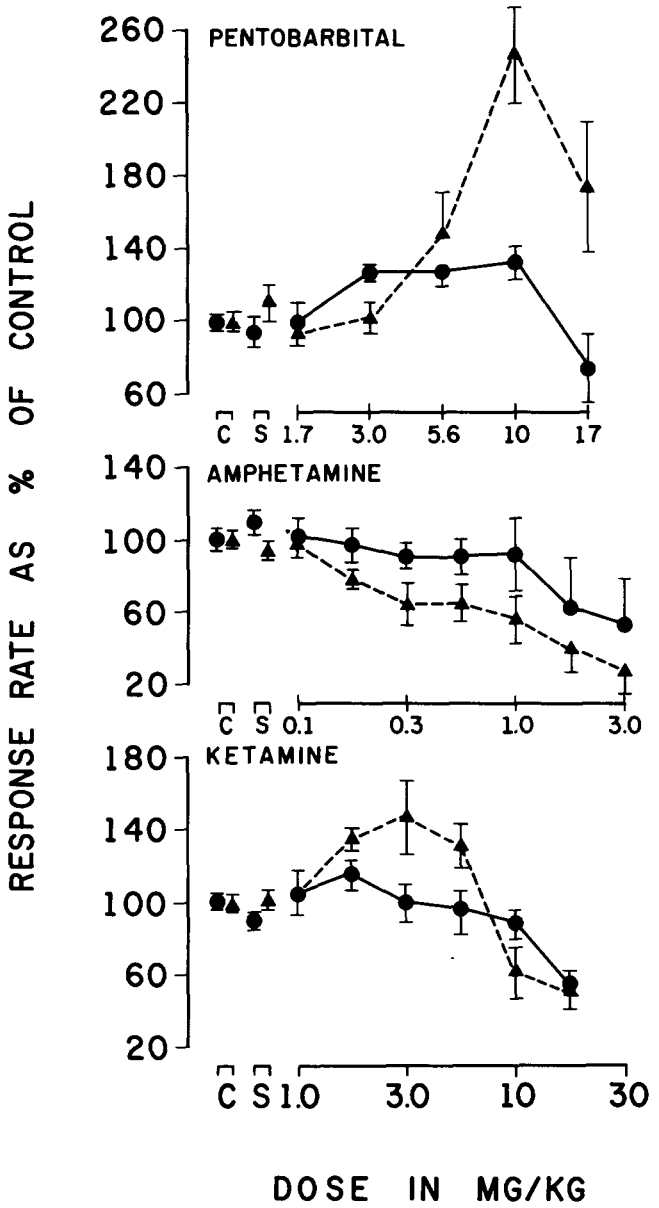

FIG. 1. Drug effects on overall rates of punished (▲) and unpunished (●) responding of pigeons under the mult FI5 FI5(shock) schedule. In the punishment component every response, except the reinforced one, produced an electric shock. Each point in the dose-response curve for pentobarbital and amphetamine represents the mean of duplicate determinations in three animals (P6, P10 and P11), and in four pigeons (the formers and P8) in the ketamine dose-response curves. The points for saline injections (S) were similarly calculated. The mean (made equal to 100%) and the variation of undrugged controls (C) were calculated from eight observations for each bird, made during the corresponding dose-response determination period and in the three days immediately preceding it. Vertical bars represent ± SEM.

a consequence, overall response rates in the two schedule components were markedly different (Table 1).

Drug Effects on Overall Rates of Punished and Unpunished Responding

The three drugs studied exerted differential effects in the two components of the multiple schedule, as shown by the dose-response curves in Fig. 1. Doses from 3 to 10 mg/kg of pentobarbital moderately increased overall response rates in the unpunished component of the multiple schedule, whereas 17 mg/kg of the drug decreased responding. Increases in punished responding were apparent after 5.6 mg/kg of pentobarbital, very marked following 10 mg/kg and were still present, though quite variable, after 17 mg/kg of the drug.

Amphetamine, at doses ranging from 0.17 to 3 mg/kg, decreased punished responding in proportion to the injected dose. In contrast, unpunished responding was unaffected by doses from 0.1 to 1 mg/kg and less decreased than punished responding by 1.7 and 3 mg/kg of amphetamine.

Ketamine differed from both pentobarbital and amphetamine in its effects on punished and unpunished responding in the mult FI5 FI5 (shock) schedule. Ketamine administration increased only slightly overall rates of unpunished responding at the dose of 1.7 mg/kg. On the other hand, only the dose of 17 mg/kg produced a clearcut decrease in unpunished response rates, intermediate doses being ineffective. On punished responding, however, both the rate-increasing and the rate-decreasing effects of ketamine were larger and extended through a broader range of doses. Moderate increases in punished responding were caused by 1.7, 3 and 5.6 mg/kg, whereas rate decreases of similar extent occurred after the administration of 10 and 17 mg/kg of ketamine.

DISCUSSION

Although similarities have been reported between the behavioral effects of ketamine and amphetamine [25,26], the present results show that the two drugs affect punished responding in different ways. While ketamine had a biphasic effect on the overall response rates in the punished component of the multiple schedule, increasing at low doses and decreasing at high doses, amphetamine caused only dose-dependent decreases in punished responding. This last effect of amphetamine conforms with a large body of evidence showing that amphetamine-like drugs either do not enhance or decrease low rates of responding suppressed by response-contingent electric shock [11, 13, 18]. In contrast, amphetamine tends to increase low response rates generated by other procedures [2, 8, 9, 14, 15, 16, 17, 21, 23, 25, 26].

The magnitude of the facilitatory effect of ketamine on punished responding shown by the present results was moderate as compared to the effect of pentobarbital. Nevertheless, using similar experimental conditions, McMillan [18] reported facilitatory effects of three benzodiazepines, chlordiazepoxide, diazepam and oxazepam on punished responding which were of comparable magnitude to those presently caused by ketamine. Since the benzodiazepines are among the most effective agents releasing punished behavior under several experimental conditions [22], it may be concluded that the effects of ketamine on punished responding are similar to those of minor tranquilizers. However, a recent study by Wenger (personal communication), in which a mult FR FR(shock) schedule was used, evidenced facilitatory effects of ketamine and phencyclidine on FR punished behavior in the pigeon that were very small in comparison to those of pentobarbital and extended only over a narrow range of doses. In addition, the present and McMillan's [18] studies show that the pattern of ketamine action on punished and unpunished FI responding is different from that of

pentobarbital and other minor tranquilizers. Whereas high doses of pentobarbital and of benzodiazepines decreased overall rates of unpunished FI responding, while still increasing or not affecting punished responding, high doses of ketamine decreased punished responding to the same extent or even more than unpunished FI rates.

Therefore, the present as well as Wenger's ([24] and personal communication) results show that ketamine facilitates punished responding, a distinctive feature of minor tranquilizers. Since ketamine has also been shown to induce amphetamine-like effects on mult FI FR responding [25,26], the conclusion may be drawn that ketamine causes characteristic effects on schedule controlled behavior.

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