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# The Effects of Phencyclidine and Ketamine on Sensory Thresholds and Reaction Times in the Baboon[1]

SCOTT E. LUKAS,[2] ROBERT D. HIENZ[3] AND JOSEPH V. BRADY

*Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine Baltimore, MD 21205*

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LUKAS, S. E., R. D. HIENZ AND J. V. BRADY. *The effects of phencyclidine and ketamine on sensory thresholds and reaction times in the baboon.* PHARMACOL BIOCHEM BEHAV **23**(5) 743–747, 1985.–Adult male baboons were trained on a reaction time procedure, and absolute thresholds and reaction times to both a 16.0 kHz pure tone and a white light were obtained. Acute IM injections of phencyclidine (0.0032 to 0.1 mg/kg) or ketamine (0.032 to 3.2 mg/kg) were given at the beginning of 2-hr test sessions. Phencyclidine had no effect on auditory thresholds, visual thresholds, or visual reaction times, but selectively elevated auditory reaction times. Ketamine, on the other hand, elevated auditory thresholds and both auditory and visual reaction times, while having no effect on visual thresholds. Ketamine was also less potent than phencyclidine in elevating auditory reaction times, and recovery from these impairments was evident during the two-hour test sessions for ketamine, but not for phencyclidine.

Phencyclidine PCP Ketamine Psychophysics Vision Hearing Baboons Primates

PHENCYCLIDINE was introduced by Greifenstein *et al.* [6] into anaesthetic practice because of its unique ability to produce anesthesia without causing a loss of consciousness. During recovery, the emergence of frightening behavioral disturbances precluded its use in general medicine. Phencyclidine is no longer available as a therapeutic agent, but has become a widespread drug of abuse [16,20]. A shorter-acting analogue, ketamine, is however, used in pediatrics and veterinary practice.

The precise mode of action of phencyclidine and its analogues is unknown. Early studies by Greifenstein *et al.* [6], Beech *et al.* [1], and Morgenstern *et al.* [14] suggested that the disruption of psychological function was primarily a result of altered sensory reception. Disturbances in cognition were reported to resemble those of thought-disordered schizophrenics [5,12], and the overall clinical toxicity of phencyclidine was presented by Showalter and Thornton [19].

The development and refinement of laboratory procedures for measuring psychophysical function [2,21] have provided the framework for evaluating drug-induced changes on sensory and motor function. The detection of such changes in basic sensory and motor functions is necessary before the proper evaluation of drug effects on more complex perceptual or cognitive processes can be made. Previous reports from this laboratory [3, 8, 9] have characterized the effects of various stimulants and depressants on auditory and visual thresholds and reaction times in unrestrained baboons. The aim of the present report was to study the dissociative anesthetics phencyclidine and ketamine at doses that have been previously shown to be self-administered by the baboon [13].

## METHOD

### *General Procedure*

The psychophysical methodology used has been previously described [9]. Briefly, baboons were trained to press a lever and hold it depressed for varying intervals until presentation of a light flash or tone burst signalled the availability of a food reinforcer following lever release. Correct responses were defined by lever releases occurring during the 1.5 sec stimulus duration, and were reinforced with banana-flavored food pellets. Detection thresholds were determined by systematically varying the stimulus intensity and recording the frequency of correct and incorrect responses. In addition, response latencies (i.e., elapsed time between signal onset and lever release) were recorded to the nearest millisecond as a measure of reaction time.

### *Subjects and Apparatus*

The subjects were 8 dog-faced baboons (*Papio anubis*), housed in individual cages and maintained on a 22-hour restricted feeding schedule with supplemental monkey chow

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[2]Present affiliation: Alcohol and Drug Abuse Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02178.

[3]Requests for reprints should be addressed to Dr. Robert D. Hienz, Division of Behavioral Biology, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Baltimore, MD 21205.

and fresh fruit provided on a daily basis after each experimental session. The testing apparatus consisted of a modified baboon squeeze cage fitted within a double-walled sound attenuating chamber (IAC-1201A). A 76×97 cm intelligence panel attached to one side of the cage contained a primate lever (BRS/LVE model PRL-003), a red light-emitting diode used as a cue light, a 2.5 cm diameter translucent Plexiglas visual stimulus patch, and a tube feeder for delivery of banana pellets. As the animal faced the panel the cue light and visual stimulus patch were at eye level, the feeding tube at mouth level, and the response lever at waist level in front of the right arm.

Auditory stimuli were generated by an oscillator (Krohn-hite, Model 4141R) passed through an electronic switch (Coulbourne, Model S84 with 20 msec rise and fall times), programmable attenuator (Coulbourne, Model S85-08), amplifier (Crown D-60), and finally through a wide range speaker (FMI custom made). The speaker was suspended outside the cage and located directly over the animal's head, approximately 20 cm above ear level. The light source for the visual stimuli was a slide projector mounted on the outside of the chamber which projected white light onto the back of the stimulus patch through an otherwise light tight aperture in the chamber wall. Stimulus intensity was varied by using neutral density filters graded in half-log steps in the slide projector. Light intensities were calibrated with a light meter (United Detector Technology, model 40X).

Programming of the experiments was accomplished with a Coulbourne solid-state control system. Data recording involved the use of electromechanical counters and a microprocessor that recorded all response latencies and computed median latency and the first and third quartiles. Animals were also observed via a closed-circuit infrared TV monitoring system.

*Procedure*

The sequence of events during a trial was as follows: In the presence of a flashing red cue light (5/sec), a lever press changed the flashing red light to a steady red light which remained steady as feedback as long as the animal held the lever down. At intervals ranging from 1.0 to 7.3 sec after initiation of this maintained holding response, a stimulus (white light on the circular patch or tone burst through the speaker) was presented for 1.5 sec. Release of the lever within the 1.5 sec stimulus interval delivered a single banana pellet and initiated a 1 sec intertrial interval (ITI) during which no stimuli were presented and additional lever responses re-initiated the ITI. Thus, a 1 sec response-free period was required before the next trial could occur. Incorrect responses (i.e., lever releases prior to stimulus onset) reinstated the 1 sec ITI without reinforcement. Following the 1 sec ITI, the flashing red cue light signalled initiation of the next trial in the series of several hundred which comprised each daily two to three hour experimental session. Stable baseline levels of performance on this procedure typically required two to three months of daily training sessions.

Auditory and visual thresholds were measured during separate sessions, and were determined by randomly varying the intensity of the test stimuli from trial to trial and examining detection frequencies (i.e., correct lever releases/total trials) at each intensity. For the auditory modality, four intensity levels (10 dB apart) of a 16.0 kHz pure tone were used, with the lowest level set just below an animal's estimated threshold. For the visual modality, the four intensity

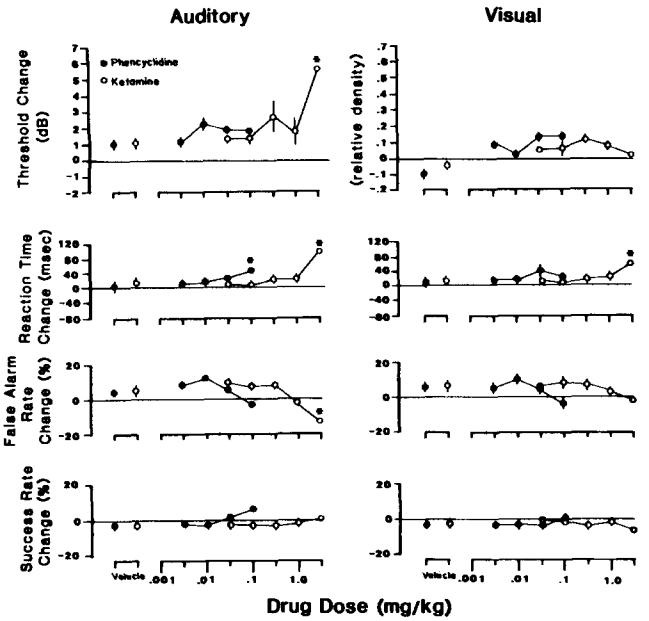


FIG. 1. The effects of acute IM injections of phencyclidine and ketamine on changes in auditory and visual thresholds, median reaction time of correct lever releases, catch trial rates and success rates. Values are means±one standard error of 3 subjects. Only two of three subjects responded at the 3.2 mg/kg ketamine and 0.1 mg/kg phencyclidine (auditory only) doses. *Indicates means significantly different from vehicle control data at $p<0.05$.

levels of white light were 0.5 neutral density filter units apart, with the lowest level set just below an animal's estimated threshold. For both auditory and visual threshold testing, occasional "catch" trials (no-stimulus trials) were interspersed among the normal trials; these catch trials served to measure false alarm or "guessing" rates.

For both the auditory and visual threshold determinations, each test session was divided into blocks of 140 trials with each of the four intensity levels plus catch trials presented randomly approximately 28 times during each block. Four to five such blocks of trials occurred within each session, providing a number of independent within-session estimates of the sensory threshold and functions relating reaction time to intensity. Sensory thresholds were determined from percent correct detections at each intensity by interpolating to the intensity that produced a detection score halfway between the false alarm rate and 100%. Thresholds were considered stable for a session when the threshold estimates for all test blocks within a session varied by no more than ±0.15 log density units for visual thresholds, and by no more than ±2 dB for auditory thresholds. In both cases, such a determination of threshold stability required a false alarm rate below 30% and no systematic changes in the data. Since reaction times are typically skewed due to the physiological limits on lever release time, the standard measure of central tendency employed was the median. Reaction times were considered stable when the shortest and longest median reaction times for the highest stimulus intensity differed by no more than 50 msec over all test blocks of a session. The proficiency of each animal's lever-holding behavior was also measured, defined as the percentage of trials within each test block during which an animal released the lever only after

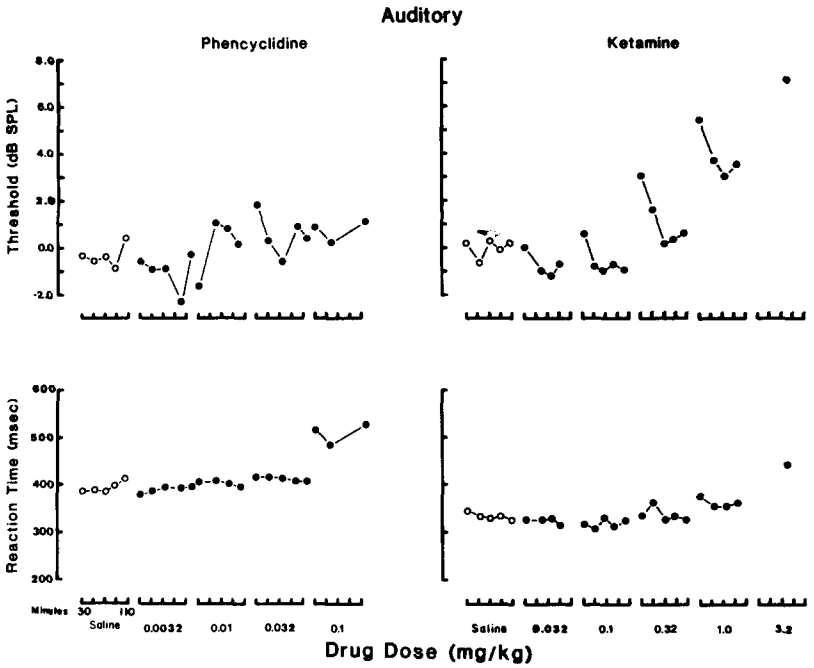


FIG. 2. Time course of within session phencyclidine- or ketamine-induced changes in auditory thresholds and median reaction times for two baboons. Each point represents values obtained from 140 stimulus presentations in each of 4–5 blocks per session. Time is in minutes after injection.

test stimulus onset (termed "success" rate in results). All data were analyzed using a repeated measures analysis of variance. Significant differences from baseline control data were then determined using Dunnett's test for differences from control means.

*Drugs*

The following drugs and doses (mg/kg) were dissolved in saline and administered intramuscularly in the gluteal region: phencyclidine hydrochloride (0.0032, 0.01, 0.032, 0.1, 0.32) and ketamine hydrochloride (0.032, 0.1, 0.32, 1.0, 1.8, 3.2). All drug concentrations were adjusted such that the injection volume was maintained between 0.05 and 0.15 ml/kg. The actual injection site was varied in order to prevent tissue damage from multiple injections. Injections were given at the beginning of each experimental session, immediately before placing the animal in the chamber. A 15 min dark adaptation period and a 15 min "warm up period, which consisted of one block of 140 trials, ensued before formal threshold determinations were begun. Doses of drug were given in a mixed order, and subsequent drug administrations were scheduled only after all performance criteria (i.e., thresholds, reaction times, false alarm rates) returned to baseline values and no systematic trends in the data were evident.

## RESULTS

Figure 1 summarizes the basic effects of phencyclidine and ketamine in the present study, showing the effects of these two drugs on auditory and visual thresholds and their respective reaction times, false alarm rates, and success rates. Each point represents the mean of the individual animal means for each measure. Individual means were based on differences between the peak drug effect and the mean of all blocks of the preceding saline control day averaged across replications at each dose, where the peak drug effect is defined as the highest single value of a measure found across all blocks of a drug session (lowest value for success rates only). Vehicle control data were derived in a identical manner. Phencyclidine did not significantly affect either auditory or visual thresholds across the dose range from 0.001 to 0.1 mg/kg. Phencyclidine also had little effect on reaction times, significantly lengthening auditory reaction times only at the 0.1 mg/kg dose and having no effect on visual reaction time across this dose range. With one exception, all animals stopped responding at the 0.32 mg/kg dose of phencyclidine during auditory and visual threshold testing. The one exception responded during visual threshold testing at this dose, showing highly significant elevations in visual thresholds (a 0.7 relative density elevation) and visual reaction times (a 100 msec reaction time elevation). For all animals, both false alarm rates and success rates showed no significant changes across the dose range studied.

Ketamine, on the other hand, produced significant elevations in auditory thresholds at the 3.2 mg/kg dose without affecting visual thresholds at any of the doses tested. Ketamine also significantly lengthened both auditory and visual reaction times at the 3.2 mg/kg dose, thus being about 30 times less potent than phencyclidine in producing auditory reaction time changes. Like phencyclidine, ketamine had no effect on success rates. Auditory false alarm rates, however, were significantly lower at the 3.2 mg/kg ketamine dose. Since threshold determinations were corrected for

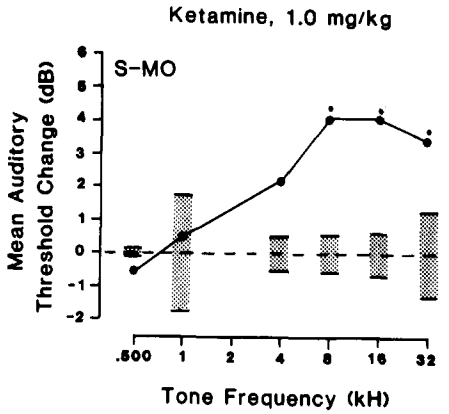


FIG. 3. Mean auditory threshold change as a function of tone frequency following 1.0 mg/kg ketamine. Shaded areas represent ±1 S.D. about the means of the saline control sessions. *Indicates significant differences at $p<0.05$.

changes in false alarm rates, the observed elevations in auditory thresholds were not due to any fluctuations in the false alarm rate. Lower false alarm rates would, in fact, result in lower auditory thresholds.

Figure 2 shows the time course of within-session changes in auditory thresholds and median reaction times for both compounds in 2 baboon subjects. Over the approximately 2-hr session, no variations were apparent during vehicle control sessions. Transient, within-session fluctuations in auditory thresholds occurred after the lower doses, and reaction times were remarkably stable throughout the sessions. There was, however, a 29% increase in reaction time at the 0.1 mg/kg dose of phencyclidine that persisted throughout the 2-hr session in the absence of significant effects on auditory thresholds. In contrast, ketamine impaired auditory sensitivity by 40 to 60% after doses of 0.32, 1.0, and 3.2 mg/kg. Ketamine produced its maximal disruption of auditory sensitivity within 1 hr after injection. During the rest of the session auditory thresholds showed evidence of recovery. These transient changes in auditory thresholds occurred in the absence of significant changes in reaction times, except after the highest dose of ketamine (3.2 mg/kg).

Ketamine's effects on auditory thresholds were more closely examined in an animal that clearly demonstrated these effects. The drug's effects were determined using a number of pure tone frequencies across the hearing range of baboons. Figure 3 shows mean auditory threshold change as a function of tone frequency following 1.0 mg/kg ketamine, with shaded areas representing ±one standard deviation about the means of saline control sessions. Significant threshold elevations occurred for this ketamine dose at frequencies of 8 kHz and above (starred points, $p<0.05$), while at the lower tone frequencies no such changes were evident.

## DISCUSSION

The results of the present study indicate that phencyclidine and ketamine have different profiles of effects on sensory and motor function in baboons. Phencyclidine significantly elevated auditory reaction times while having no effect on visual reaction times or auditory and visual thresholds across the same dose range. Ketamine similarly lengthened auditory reaction times, but also lengthened visual reaction times. Additionally, ketamine significantly elevated auditory thresholds and did so in a frequency-specific fashion, elevating thresholds for pure tones of 8 kHz and above but not for lower frequency tones.

The selective effects of these two compounds on each of the two sensory modalities is curious considering that phencyclidine and ketamine share virtually similar pharmacologic profiles in numerous other assays [11, 17, 18]. The relative potencies (i.e., phencyclidine approximately 30× greater) obtained in the present study do, however, agree with other reports in the literature [7, 10, 18]. In a previous study [9] we reported that pentobarbital elevated auditory reaction times but had little effect on auditory thresholds, effects similar to those of phencyclidine. Unlike phencyclidine, however, pentobarbital also markedly elevated visual thresholds and reaction times.

The observed differences in sensitivity may be related to the two drugs' different pharmacokinetic profiles. After high doses of phencyclidine (0.32 mg/kg), most animals failed to respond at all during the entire session. Conversely, ketamine's effects of suppressing responding at 3.2 mg/kg dissipated within an hour, permitting the animals to respond before the session ended. Thus, the data from ketamine represent a recovery response, whereas phencyclidine completely disrupted performance at these high doses.

Possible causes for the changes in visual reaction times found with ketamine include changes in hand position, pupillary diameter, or non-specific effects on the eye muscles such as nystagmus. Direct observation of the animals via video camera, however, did not reveal any postural changes during testing. Further, these and more subtle movements such as head movements or eye closures might be expected to affect detection frequencies for all of the low-level visual stimuli employed. No such effects were observed. Pupillary constriction could be expected to reduce visual stimulus intensity impinging on the retina, thereby elevating visual thresholds and lengthening visual reaction times. Since the ketamine-induced lengthening of reaction times was not accompanied by visual threshold elevations, these changes could not be due to simple pupillary constriction. The elevated auditory thresholds following ketamine administration also suggest the operation of at least 2 mechanisms for this drug, since any simple mechanism for motor impairment cannot account for the frequency-specific effects of the drug in elevating auditory thresholds (Fig. 3). The restriction of ketamines effects to high frequencies is also reminiscent of the known effects of aminoglycoside antibiotics such as kanamycin, which affect high-frequency hearing first by progressively destroying hair cells starting at the basal end of the cochlea [22].

In a previous study using Rhesus monkeys as subjects, phencyclidine was reported to produce dose-dependent increases in response latencies in a scaled visual size-acuity procedure [4]. This profile essentially mimicked that of pentobarbital in the same study. In human subjects, phencyclidine has been reported to produce general sensory impairment as measured by tests designed to evaluate the various sensory modalities [14]. While two-point discriminations and touch thresholds were most affected, auditory sensitivity and visual acuity were also affected. Regardless of the exact nature of the different sensory profiles exhibited by these two compounds, they are discriminable from one another using a drug discrimination paradigm [15]. This difference was observed only during certain conditions when one drug was used to train the rats while the other one was

used for testing. This differential discriminability may relate to the different profile of sensory impairment observed in the present study.

In conclusion, the present study demonstrated that phencyclidine and ketamine produced differential changes in sensory and motor function. Each drug had its own characteristic profile with respect to potency and duration of action. These differences may reflect subtle differences between these two compounds with respect to their effects on an animal's ability to process and react to incoming stimuli.

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