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The Effects of Pentobarbital upon Auditory and Visual Thresholds in the Baboon[1]

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HIENZ, R. D., S. E. LUKAS AND J. V. BRADY. *The effects of pentobarbital upon auditory and visual thresholds in the baboon.* PHARMAC. BIOCHEM. BEHAV. 15(5) 799–805, 1981.—Adult male baboons were trained to perform a reaction time procedure, which required holding a lever depressed for varying time intervals and releasing it during a 1.5 sec test stimulus to receive food. The test stimulus was a 16 kHz tone for auditory threshold testing, and a white light for visual threshold testing. Stimulus intensities were randomly varied to determine detection thresholds, and the latency of each correct lever release was recorded as a measure of reaction time. Acute, IM injections of pentobarbital (1.0 to 17.0 mg/kg) were given at the beginning of 2-hr experimental sessions. Pentobarbital elevated the absolute visual threshold and increased both auditory and visual reaction times in a dose-related manner. Two of three baboons showed reaction time and visual threshold decrements at pentobarbital doses which produced no change in absolute auditory thresholds.

Pentobarbital Auditory threshold Visual threshold Reaction time Primates

THE effects of drugs upon complex perceptual processes have provided the focus for an expanding research literature over the past two decades [13,16]. For the most part, however, the contribution of changes in basic sensory functions to such effects has been difficult to determine because of the diverse procedures employed and the complex performance processes involved. Opiates, barbiturates, and benzodiazepines for example, have all been reported to impair visual pattern recognition and/or motor performance [2, 19, 22, 23] and decrements in both visual and auditory discrimination performances have been described following administration of hallucinogens [7, 9, 14]. To the extent that such drug effects may involve changes in basic sensory functions (e.g., absolute visual and/or auditory thresholds and intensity, frequency or wavelength difference limens) however, it is of some importance to determine more directly the effects of pharmacological agents upon these functions.

The development and refinement of laboratory measurement techniques over the past decade have provided methodologies of demonstrated sensitivity and reliability for the quantitative assessment of psychophysical functions in man and across a range of other animals [6, 8, 17, 25]. Using these procedures, the ototoxic effects of both salicylates [18] and kanamycin [24] on auditory functions in humans and non-human primates have been described, and imipramine color blindness has been reported in pigeons [10]. Auditory threshold shifts following administration of *d*-amphetamine [5] quinidine, and kanamycin [1] have also been documented under such conditions, and similar drug-induced changes in visual thresholds have been reported with LSD-25 [3], and pilocarpine [1].

Previous reports from our laboratory have described preliminary studies of effects upon visual and auditory thresholds in baboons of several behaviorally-active stimulants and depressants [4, 11, 12, 15]. The present study was designed to provide a more detailed analysis of the effects of pentobarbital upon absolute auditory and visual thresholds and reaction times in laboratory baboons.

METHOD

General Procedure

The psychophysical methodology involved the use of a reaction-time procedure which required the baboons to press a lever and hold it depressed for varying intervals until presentation of a light flash or tone burst lasting 1.5 sec signalled the availability of a food reinforcer following lever release. Correct responses were defined by lever releases occurring during the 1.5 sec stimulus 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 (i.e., lever releases occurring prior or after the 1.5 sec stimulus). 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.

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Subjects and Apparatus

The subjects were three dog-faced baboons (*Papio anubis*), housed in individual cages and maintained on a 22-hr restricted feeding schedule with supplemental monkey chow 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 LED cue light, a 2.5 cm diameter opaque Plexiglas visual stimulus patch, and a tube feeder for delivery of banana pellets. With the animal positioned facing 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. A wide-range speaker (FMI custom-made) suspended outside the cage and located directly over the animal's head approximately 20 cm above ear level provided for the delivery of auditory signals. Animals were observed via a closed-circuit infrared T.V. monitoring system.

The light source for the visual stimuli was provided by a slide projector mounted on the outside of the chamber which projected white light on to 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 in the slide projector. Light intensities were calibrated with a light meter (United Detector Technology, Model 40X). Acoustic signals were generated by an oscillator (Krohn-Hite, Model 4141R) passed through an electronic switch (Coulbourne, Model S84—20 msec rise and fall times), programmable attenuator (Coulbourne, Model S85-08), amplifier (Crown D-60), and finally, through the wide range speaker. The system was calibrated with a Brüel and Kjaer Model 2603 microphone amplifier and 1.25 cm condenser microphone (Type 4133) located at ear level and at 0° incidence to the speaker. Programming of the experiments was accomplished with a Coulbourne solid-state control system. Data recording involved the use of electromechanical counters and a microprocessor interfaced to a video terminal which recorded all response latencies and computed median latency and first and third (Q) values.

Procedure

Following initial shaping of lever pressing and discrimination of the holding and release components of the response, all animals were introduced to the discrete trial reaction time procedure. 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 switch in the closed position. 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, so that a 1-sec response-free period was required before the next trial could occur. Incorrect responses (i.e., lever presses prior to stimulus onset or after the 1.5 sec stimulus interval) 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 determined by randomly varying (in accordance with the method of constant stimuli) the intensity of the test stimuli from trial to trial and examining detection frequencies (i.e., correct lever releases) 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 the animal's estimated threshold. For the visual modality, four intensity levels (0.5 log density units apart) of the white light were used with the lowest level set just below the animal's estimated threshold. Interspersed among both the auditory and visual test trials were a series of "catch" trials during which no stimulus was presented to measure the false alarm or "guessing" rate.

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 which provided a number of independent within-session estimates of the sensory thresholds and functions relating reaction time to intensity. Sensory thresholds were determined from percent correct detections at each intensity by interpolating to the intensity which produced a detection score halfway between the catch trial rate and 100%. Stable thresholds were based upon determinations from at least three successive test blocks with estimates which 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 catch trial rate below 30% and no systematic change trends in the data. Reaction time was typically skewed due to the physiological limits on lever release time. Thus, the standard measure of central tendency employed for such distribution was the median, with variability reported in terms of the interquartile range. The criterion for stability in reaction times was at least three successive test blocks with reaction times to the highest stimulus intensity varying by no more than 50 msec.

Because of poor solubility and stability in aqueous solutions, pentobarbital was dissolved in a vehicle containing equal parts of physiologic saline and propylene glycol. The drug concentration was adjusted such that the injection volume was maintained between 0.05 and 0.15 ml/kg. All injections were given intramuscularly in the gluteal region, and the actual injection site was varied in order to prevent tissue damage resulting from multiple injections.

Injections of pentobarbital, saline, or vehicle 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" session ensued before formal threshold determinations were begun. Doses of pentobarbital were given in a mixed order, and subsequent drug administrations were scheduled only after all performance criteria (i.e., thresholds, reaction times, catch trials, etc.) returned to baseline values and no changing trends were evident in the data.

RESULTS

Figure 1 illustrates the dose-dependent effects of pentobarbital upon auditory and visual thresholds, median reac-

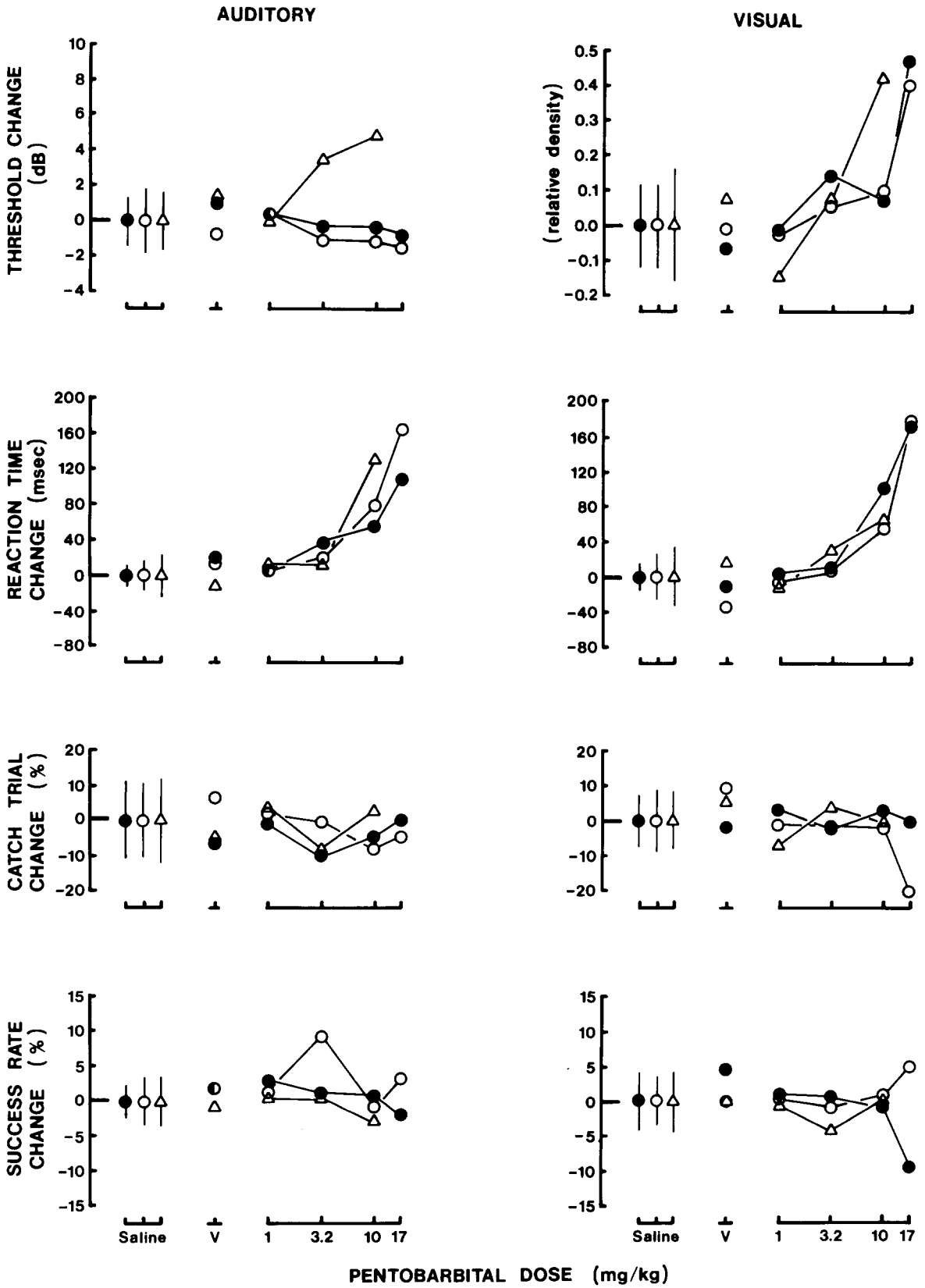

FIG. 1. The effects of acute IM injections of pentobarbital upon auditory and visual thresholds, median reaction time of correct lever releases, catch trial rates and success rates for animals PE (○), MO (△), and IK (●). Data points represent the average differences between drug values and the corresponding saline values on the preceding day. "V" represents data obtained from vehicle alone.

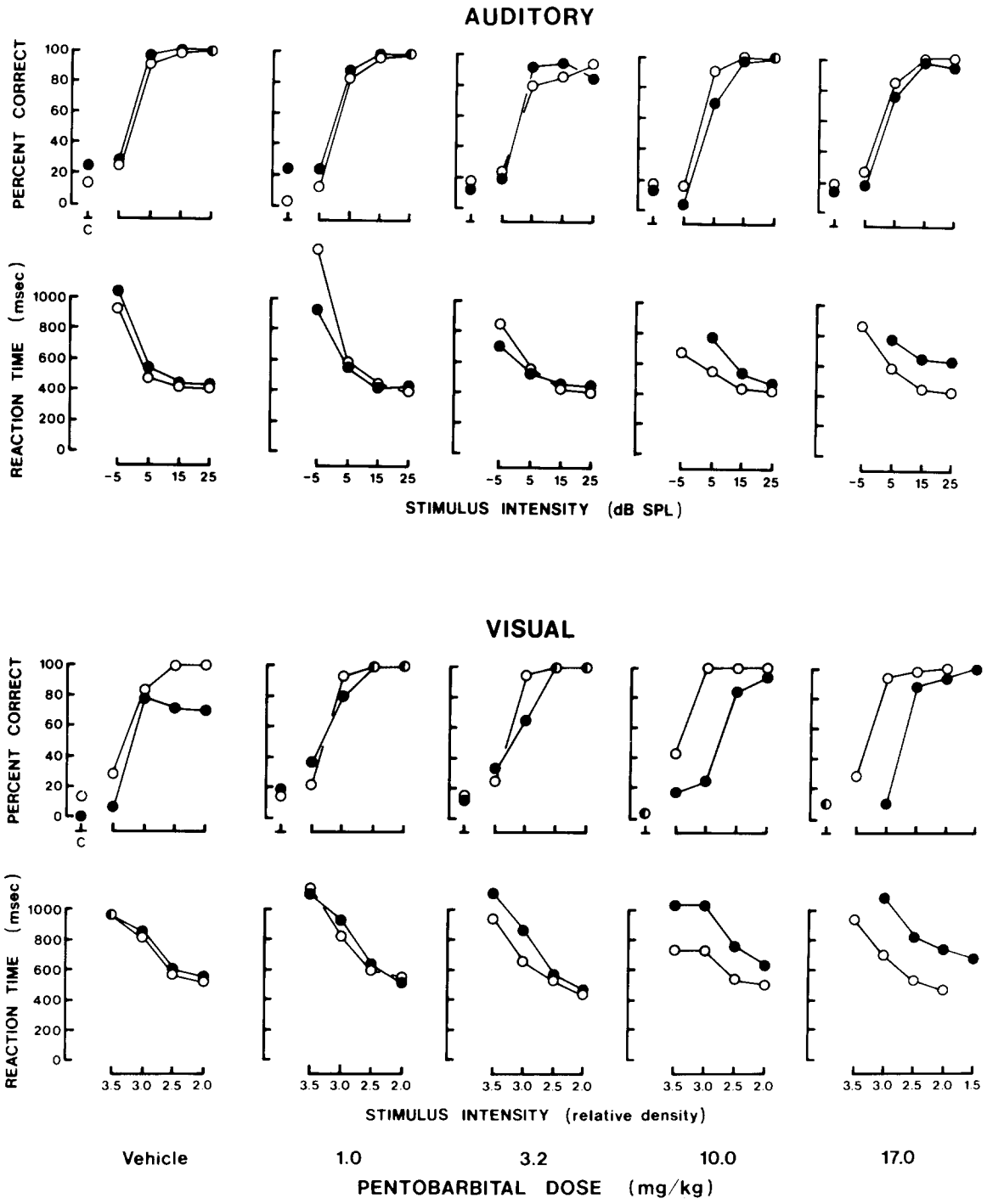

FIG. 2. Auditory and visual psychometric functions and reaction time functions during peak drug effect for animal IK. Closed circles (●) represent pentobarbital values while open circles (○) represent saline values. "C" represents the percent responses to catch trials.

tion times for correct releases, catch trial rates, and success rates for three animals. All data points are the average of at least two determinations with each animal at each dose, and represent the difference between those values at peak drug effect time and the corresponding saline values during the preceding day's control session. Reaction time values are for auditory stimuli presented at approximately 25 dB above the auditory thresholds, and for visual stimuli presented at approximately 1.25 log relative density units above the visual thresholds. The success rate is defined as that percentage of trials completed in each block without a lever release prior to test stimulus onset, and thus indicates the proficiency of the

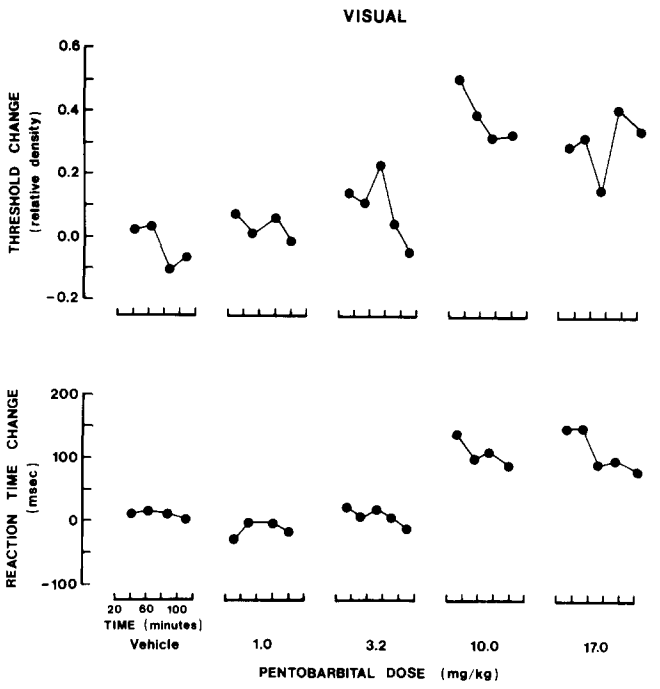

FIG. 3. Time course of within session pentobarbital-induced changes in visual thresholds and median reaction times for animal IK.

lever holding response during experimental sessions. The 95% confidence limits of the variability for all saline sessions preceding a drug session are shown to the left in each graph for each animal. Also shown are values obtained following vehicle alone administration (marked "V").

All three animals demonstrated consistent elevations in the visual threshold and reaction times to both visual and auditory stimuli following doses of 10.0 and 17.0 mg/kg. With two of the three animals however, no change in the auditory threshold was apparent over this same dose range. A third animal (MO) did show a slight elevation in the auditory threshold at both the 3.2 and 10.0 doses, though the sensitivity of this animal to the drug prevented higher dose determinations since the 17.0 mg/kg dose of pentobarbital completely suppressed responding. For the most part, both catch trial rates and success rates were unaffected over the dose range studied, though at the highest dose, decreases were observed in the visual catch trial rate for animal PE and the visual success rate for animal IK.

Figure 2 shows sample auditory and visual threshold and reaction time functions during the time of peak drug effect for animal IK over the dose range from 1.0 to 17.0 mg/kg pentobarbital. Percent correct lever releases and reaction times are plotted as a function of stimulus intensity in dB sound pressure level (SPL) for the auditory determinations and in log relative density units for the visual determinations. The saline data points were similarly derived from the control sessions conducted on days preceding each drug session. At the highest dose, pentobarbital produced different effects upon auditory and visual thresholds even though similar increases in reaction times to both auditory and visual stimuli occurred. At 17.0 mg/kg, a clear shift in the visual threshold function (lower section, Fig. 2) occurred in the absence of any change in the auditory threshold function (upper section, Fig. 2) under identical drug conditions. Parrallel drug-induced increases in both the auditory and visual reaction time curves were evident.

Figure 3 shows the time course of within-session changes in visual thresholds and median reaction times for animal IK as a function of pentobarbital dose. Over the approximately 2-hr session, no significant variations were apparent during vehicle control sessions or at the lowest pentobarbital doses. The transient elevation in the visual threshold observed approximately one hour after administration of 3.2 mg/kg pentobarbital dissipated within 30 min and occurred in the absence of any change in reaction time. The more pronounced changes in both visual thresholds and reaction times after the 10.0 and 17.0 mg/kg doses, however, endured over more extended segments of the session with some recovery apparent over the 2-hr time course at the 10.0 mg/kg dose. At the highest dose, the visual threshold remained elevated throughout the two-hour course of the session though some recovery of the initially elevated reaction times were observed by the end of the session.

DISCUSSION

The results of this study show clearly that acute, IM injections of pentobarbital elevate the absolute visual threshold and increase both auditory and visual reaction times in a dose-dependent manner. These effects were consistently observed with all three animals in the study over a pentobarbital dose range from 1.0 to 17.0 mg/kg. Moreover, with two of the three baboons, the drug-induced decrements in the visual threshold and reaction times occurred in the absence of any change in the absolute auditory threshold. The 4–5 dB elevation in the auditory threshold shown by the third animal is not typically considered a significant hearing loss in humans.

The fact that increases in auditory reaction time were observed in the absence of any change in absolute threshold, suggests that the elevations in the visual threshold at the higher pentobarbital doses of 10.0 and 17.0 mg/kg can not be explained simply in terms of drug-induced lengthening of reaction times resulting in fewer correct responses at the lower stimulus intensities. Estimates of the largest threshold elevations which hypothetically could be attributed to drug-induced reaction time increases (e.g., 0.1 to 0.15 relative density units) fall far short of the magnitude of visual threshold elevations observed in these studies (i.e., 0.2 to 0.6 relative density units). Moreover, it has been previously demonstrated that the reaction time procedure produces absolute threshold functions nearly identical with other psychophysical procedures for both man and monkey [20], when incorrect responses are defined as latencies longer than 1000 msec. Finally, the relative independence of the threshold and reaction time measures in this procedure has been demonstrated in a series of experiments [12] showing that *d*-methylamphetamine-induced elevations in the visual threshold occur in the presence of *decreased* reaction times, and that noise-induced elevations in the auditory threshold occur in absence of any change in auditory reaction time.

The measured elevations in the visual threshold following the higher doses of pentobarbital in the present study are not easily explained on the basis of any of the known direct or indirect effects of the drug on central or peripheral processes. With regard to the possibility that sedative-like ef-

fects, for example, may have produced postural changes which altered the animal's orientation to the stimulus source during drug sessions, observations via video monitoring over the course of the study revealed no such deviations in head position relative to the visual stimulus patch. Moreover, such postural changes, had they occurred, could be expected to affect the auditory threshold determinations in a similar fashion, but no auditory effects were observed in either of the two animals showing drug-induced visual threshold elevations. Similarly, the likelihood that the observed changes in visual threshold could be attributed to drug-induced nystagmus or prolonged blinking seems equally remote since neither of these effects were ever observed following pentobarbital administration either in the home cage or test chamber. Furthermore, any such effects would have produced a parallel lowering of the psychometric functions due to detection failures at all stimulus levels and no such generalized effects were ever observed.

Among the possible peripheral effects of pentobarbital which could provide a plausible explanation of the visual threshold shift would be miosis. In the dark-adapted animal, even slight decreases in pupil diameter can elevate the visual threshold. Control experiments with these same baboons, for example, have shown that the application of 0.1 ml of a 1% solution of pilocarpine into each eye produced pinpoint pupils and marked elevations in visual thresholds. Significantly, however, there was no change in reaction times measured at light intensities relative to the threshold (i.e., "×" relative density units above threshold) under these pilocarpine-control conditions; this fact makes the acceptance of such a mechanism somewhat questionable as a ready explanation of the pentobarbital effects described in this report.

The fact that catch trial rates and success rates as well as auditory thresholds and detection rates at the higher visual stimulus intensities were generally unaffected at pentobarbital doses which elevated visual thresholds would tend to suggest that the observed changes were not solely related to attentional decrements produced by the drug. Nonetheless, barbiturates have been reported to impair the processing and interpretation of sensory input [2,21]. Over the dose range of 5.0 to 12.5 mg/kg pentobarbital, for example, rhesus monkeys showed dose-dependent decreases in correct responding to tachistoscopically presented stimuli as a function of systematic reductions in stimulus exposure time [2]. The findings described in the present report are over a dose range which overlaps that used in the Bartus and Johnson study [2] and suggest the possibility that an elevation in the visual threshold may have accounted, at least in part, for the central processing impairments through, for example, a rise in the sensory integration time required for retinal summation of photic stimuli. In effect, the reduced exposure durations of tachistoscopically presented stimuli could have shortened the available integration time and imposed peripheral limitations on the detection of brief visual stimuli.

Under any circumstances, the present study shows the clear effect of pentobarbital in elevating visual thresholds and lengthening both auditory and visual reaction times. These findings suggest that the interpretation of mechanisms involved in drug-induced effects upon complex perceptual processes should take into account the possible influence of such changes in basic sensory-motor functions.

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