BEHAVIORAL ASSESSMENT OF PAIN DETECTION AND TOLERANCE IN MONKEYS¹

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Cebus albifrons monkeys received electrical stimulation of the hindlimbs over a wide range of intensities. On trials signalled by a blue light, the animals were permitted to escape shock by pressing a disc, or shock was terminated after 8 sec (free escape). Escape force (disc pressure) was found to increase as stimulation intensity increased well beyond escape threshold, while shock duration curves reached plateau at the mid-range of intensities. The shock duration curves generated by free escape responses should be comparable to pain detection functions obtained by similar operations in humans, and the curves were stable over months of testing, as is generally found in pain-detection studies. On trials signalled by a red light, the animals received intense tail shock immediately after escape responses (punished escape), or, if they endured leg shock for 8 sec without escaping, then they could avoid tail shock with a panel press. The shock duration curves generated by punished escape responses should be comparable to pain tolerance functions as defined for human subjects, and the escape thresholds were considerably higher on red-light trials. As in human studies, the tolerance curves were not stable over repeated testing sessions, and some feature of the paradigm forced a progression toward extremely high levels of tolerance.

The behavioral assessment of pain in laboratory animals has progressed from the notation of a variety of reflex reactions following noxious stimulation (Carroll and Lim, 1960; Evans, 1961; Randall and Selitto, 1957; Siegmund, Cadmus, and Lu, 1957) to the measurement of aversion thresholds by operant techniques such as titration (Fields and Glusman, 1969; Weiss and Laties, 1961; Weitzman and Ross, 1962) to the realization that degree of aversiveness can be operationally defined along a continuum of responsiveness that extends over a wide range of stimulus intensities (Dinsmoor and Winograd, 1958; Campbell and Masterson, 1969; Hutchinson, Azrin, and Renfrew, 1968). These developments have

been accompanied by similar procedural advances in the study of human pain reactions, and the most powerful of these have capitalized upon the ability of human subjects to rank stimuli verbally in terms of their relative noxiousness. For example, magnitude estimation has been used to describe power functions for aversive stimuli (Hilgard, 1969; Stevens, Carton, and Shickman, 1958); and a similar approach of considerable promise has come from signal-detection theory (Green and Swets, 1966; Clark, 1969). In one type of signal-detection experiment, the subject's decision criterion or response bias is manipulated by specific instructions and can then be separated from purely sensory factors by proper treatment of the data. Without using signal-detection analyses, this paradigm has been used in the study of pain detection and tolerance in humans (Gelfand, 1964). In this procedure, subjects are instructed to report separately the onset of pain and the point at which the pain becomes intolerable, and clearly distinct thresholds result. The present study attempted to apply the above paradigm to the study of escape reactions in monkeys by establishing discrimination between trials on which there is reinforcement for not escaping electrical shock and trials on which there is no payoff for withholding escape responses.

¹This research was supported by Grant NS07261 from the National Institute of Neurological Diseases and Stroke. The research described involved animals maintained in animal-care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care. The animals' care was provided in part by N.I.H. Grant FR00421. We thank James Austin for design of electronic circuitry. During this investigation, Dr. Manning was supported by a post-doctoral fellowship from the Center for Neurobiological Sciences (Grant MH10320 from the National Institutes of Mental Health). Reprints may be obtained from C. J. Vierck, Jr., Department of Neuroscience, University of Florida, College of Medicine, University of Florida, Gainesville, Florida 32601.

Beyond the goal of discovering the extent to which escape tendencies can be controlled by manipulation of reinforcement contingencies (e.g., Weiss and Laties, 1963), it may be important to the understanding of brain mechanisms of pain perception to develop techniques of controlling the response biases of animals to produce analogues to human pain detection and tolerance functions. There is neurological and behavioral evidence that the pain continuum is not unitary but is expressed by at least two distinct conduction systems. At the periphery, there are different sets of peripheral fibers that are responsible for the perceptually distinct categories of fast, pricking, and slow, burning pain (Lewis and Pochin, 1937; Landau and Bishop, 1953; Price, 1971). Furthermore, in the central nervous system, the pain pathways can be divided into those that project directly to thalamic nuclei with specific cortical connections and those that project indirectly through the reticular formation to thalamic nuclei with diffuse cortical connections (Mehler, 1966; Albe Fessard, 1967). It appears likely that the fast, direct systems predominate at detection levels of pain, while the slow, indirect systems are predominate when pain becomes intolerable and a quality of suffering is present (Melzack and Casey, 1968). Thus, it is possible that the lability of tolerance and suffering stands in sharp contrast to the stability of detection thresholds (Barber, 1963; Beecher, 1957, 1959; Hardy, Wolff, and Goodell, 1952) because of involvement of distinct neural systems with quite different characteristics. These speculations are supported by studies with laboratory animals that have shown selective action of drugs or brain interventions on responses that occur at different stimulus intensities (Charpentier, 1968; Evans, 1961). However, in these investigations the responses differed qualitatively, and the effects may have been related directly to characteristics of the responses. The use of different sets of "instructions" to manipulate the frequency of escape responses eliminates this source of confounding.

METHOD

The subjects were three adolescent male *Cebus albifrons* monkeys. All were experimentally naive and were maintained in individual cages with free access to food and

water. During experimental sessions, each animal was restrained in a seated position in a chair constructed primarily of Plexiglas. One leg was restrained by means of a Velcro strap wrapped around the ankle and tied to a footrest. An intelligence panel was locked securely in front of the restrained animal so that the chair and intelligence panel together formed a compartment enclosing the monkey from the waist up.

After one to four weeks of adaptation to the restraining chair, all animals were initially trained to escape 24-mA leg shock. The leg electrodes were 0.6 in. (1 cm) diameter stainless steel spheres, embedded 0.6 in. (1 cm) apart in a Plexiglas strip. These were taped in position over tattooed spots on the medial calf of either leg. Leg shock stimuli consisted of 0.5-msec duration square wave pulses at 10 pulses per second, produced by a constant current stimulator supplied by a 180-V source. A warning light on the stimulator indicated voltage limiting from inadequate contact of the electrodes to the skin.

Escape training was accomplished by first making the cessation of continuous leg shock contingent upon maintaining hand contact with a 5 in. (12.7 cm) diameter aluminum disc (escape disc), which was suspended vertically in the center of the intelligence panel and connected to a Statham pressure transducer, which in turn was connected to the strain gauge coupler of a Dynagraph. Access to the disc was limited to the left hand by means of a Plexiglas shield. After an animal learned to maintain contact with the disc, a trials procedure was introduced in which trial onset was marked by an auditory click followed 1 sec later by 8-sec duration leg shock. Escape was made contingent upon pressing the disc with sufficient force to activate an electronic sensing device (Schmitt trigger), the output of which aborted the trial. The force requirement was gradually increased to a minimum force (disc pressure) of 2.4 lb (10.6 N). To preclude shock termination from startle responses and to force sampling of the stimulus, the disc was ineffective during the first second of shock; escape could occur at any time after the delay interval. Sessions of 33 trials were conducted until a criterion of three successive sessions of 85% escape responding was reached.

After criterion escape performance was es-

tablished, the disc was removed from the experimental compartment and leg shock was temporarily discontinued. Preceding these sessions, the monkeys' tails were extended through a hole in the back of the chair onto a platform with a small stock in which a shaved portion of the tail was held motionless on brass electrodes. A discriminated trials procedure was then initiated with illumination for 12 sec of either a red or blue light plus a brief click at onset. At the onset of red-light trials, a retractable lever protruded through the right side of the intelligence panel, and pressing the lever after 9 sec produced a 3-sec, 2500-Hz tone and avoided tail shock scheduled to occur simultaneously with red light termination.² Tail shock of 100-msec duration 12.5 mA ac, was generated by a constant current stimulator. The lever was not presented on blue-light trials, and tail shock was not delivered at offset of the blue light. The stimulus lights (25 W) were positioned 13 in. (33 cm) apart at the extreme upper corners of the intelligence panel. White noise was present

continuously to mask extraneous sounds. Sessions consisted of 48 presentations each of red and blue light in random order (96 trials) with a 15-sec intertrial interval.

The final stage of training led to the paradigm depicted in Figure 1 and combined the two response contingencies previously learned separately: (a) escape of leg shock by disc presses, and (b) avoidance of tail shock on red-light trials by lever presses. After an animal achieved better than 90% avoidance responses on the red-light trials described above, 8 sec of mild leg shock (0.4 mA) was scheduled to begin 1 sec after red light onset. After

²At this stage in training, one animal (#1) was food deprived to 85% of its free-feeding weight and received food reinforcers for lever responses during the last 3 sec of red light trials. This animal was introduced to the avoidance paradigm later, and transfer was rapid. The other two animals were initially trained to avoid tail shock by pressing a panel (rather than the lever) that was illuminated during the last 3 sec of red-light trials, and they were easily transferred to the lever before the final performance data were collected.

Fig. 1. Contingencies effective when an escape response was either emitted (escape) or not emitted (no escape) on free escape (blue-light) and punished escape (red-light) trials during test sessions. Forced sampling of leg shock occurred at A. Pushing the escape disc was effective in terminating leg shock only at B. Bar responses were effective in avoiding tail shock only at C. Tail shock occurred at D only if a bar response was absent.

two to five additional sessions to assure continued stability, the escape disc was returned to the experimental compartment and scheduled to be effective during the last 7 sec of leg shock. Thus, the sequence of events during a punished escape (red-light) trial was as follows: (a) red light onset with extension of the lever into the compartment; (b) after 1 sec, leg shock onset but disc pushes would not terminate shock; (c) 2 sec after light onset, disc pushes greater than 10.6 N aborted the trial, terminating the stimulus light and leg shock. If leg shock was escaped on a red-light trial, immediate tail shock was delivered and the lever was retracted. (d) If an escape response did not occur within 8 sec of leg shock (9 sec after light onset), the shock was discontinued. Lever presses during the final 3 sec of red light would avoid tail shock and would trigger the 3-sec tone, indicating safety to the animal. (e) If neither an escape response nor an avoidance response occurred, the red light went out 12 sec after onset, tail shock was delivered and the lever was retracted.

On free escape (blue-light) trials, the sequence of events was as follows: (a) blue light onset without extension of the lever into the compartment; (b) after 1 sec, leg shock onset but disc pushes would not terminate shock; (c) 2 sec after light onset, disc pushes greater than 10.6 N aborted the trial, terminating the blue light and leg shock with no further scheduled consequences on that trial; (d) if an escape response did not occur within 8 sec of leg shock, the shock and blue light were discontinued, ending the trial.

During the first two sessions of exposure to the final paradigm, the intertrial interval was increased to 60 sec and trials were reduced to 24 presentations each of red and blue light. Mild leg shock (0.4 mA) was continued over at least seven sessions to assure stability of the red-blue discrimination, and all animals achieved criterion performance of greater than 90% free escape responses (blue trials) and less than 10% punished escape responses (red trials). In the next few sessions, the maximum leg shock was gradually increased; and in the final stage of training, free and punished escape trials were presented randomly in combination with randomly varied leg shock intensities ranging from 4 to 48 mA in 4-mA steps (method of constant stimuli). Each leg was tested in blocks of five consecutive sessions.

At the beginning and end of each session, short trains of 48-mA leg shock were delivered, and the warning light on the stimulator was observed to ensure that the stimulator was delivering 48 mA through the skin.

RESULTS

The results presented in Figure 2 were obtained from five consecutive sessions following several months of testing (25 sessions on the left leg and 20 sessions on the right leg). The curves on the left side of Figure 2 present the mean latency of escape responses and the mean duration of left-leg shock endured by each animal over 10 trials of free escape and of punished escape. On free escape trials, Animals

Fig. 2. The three panels on the left give mean post-delay escape latencies (solid circles) and mean post-delay duration (open circles and squares) of left leg shock as a function of intensity of leg shock for Monkeys #1, #2, and #3. Leg shock duration is obtained by averaging together escape latencies and 7 sec for all trials on which escape did not occur. Shock duration is shown separately for blue-light or free escape trials (open circles) and for red-light or punished escape trials (open squares). Mean escape force (disc pressure) exerted as a function of leg shock intensity is plotted in the right column for free escape trials (solid squares).

#1 and #2 demonstrated response tendencies that were proportional to leg shock intensity; these animals never escaped 4 mA and always escaped intensities of 32 mA or above with short latencies. Monkey #3 consistently escaped all intensities of shock on free escape trials. In contrast, none of the animals escaped leg shock at any intensity on red-light trials, when escape would have been punished by brief tail shock. That is, all animals exhibited a preference for 8 sec of 48-mA leg shock (at 10 pulses per sec of 0.5-msec duration) to 1 sec of leg shock delivered at the same intensity followed by 100 msec of sinusoidal, 12.5-mA tail shock.

On the right side of Figure 2 the force exerted against the disc while pushing to escape shock is plotted against intensity of leg stimulation on free escape trials. These curves show that escape force increased regularly throughout the entire range of intensities delivered. The slope of the function is greatest for Animals #2 and #3, where the force more than doubles over the intensities beyond escape threshold (less than 12 mA for #2 and less than 4 mA for #3).

Not escaping on punishment trials was a pattern of behavior that developed slowly in all animals, as shown in Figure 3. These data were obtained from the second group of five sessions received on the final paradigm by Animals #2 and #3, and they preceded the data plotted in Figure 2 by 15 sessions on the left leg. Although the test situation was slightly different at this stage (see figure caption), the shock duration curves for free escape are very similar to those of Figure 2. However, the performance on punishment trials was quite different in the early and late sessions. The declining shock duration curves of punished escape responses during the early sessions (Figure 3) demonstrate a preference, at this time, of brief tail shock over long duration, high intensity leg shock.

DISCUSSION

When escape of leg shock was not punished by shocking the monkeys' tails, the average duration of leg shock varied inversely with stimulation intensity through the middle portion of the range of intensities delivered. The

Fig. 3. Mean post-delay, left-leg shock duration as a function of leg shock intensity for Monkeys #2 and #3. Shock duration on free escape (open circles) and punished escape (open squares) trials are separately plotted. These five sessions of data precede those of Figure 2 by 15 sessions of left-leg testing. During the early sessions shown here, tail shock was avoided by panel presses rather than bar presses, and leg shock was delivered by a Grass S4 stimulator and constant current unit. At this stage, Animal #1 received food reinforcers for lever responses on red-light trials, and therefore the early and late curves could not be compared directly.

major factor contributing to the form of the shock duration curves was the presence or absence of (per cent of) escape responses and not a shortening of escape latencies with increasing stimulus intensity. In contrast to plots of shock duration or escape latency, the force of escape responses increased throughout the range of intensities delivered (up to 48 mA). The force data suggest that the animals' reactions to noxious stimulation increased markedly beyond their aversion thresholds (average escape threshold of 8 mA). Therefore in behavioral studies of pain reactivity in laboratory animals, it is advisable not to restrict stimulation to values closely bracketing threshold or to restrict analysis to the frequency of escape reactions. Rather, it is important that there be a description of objectively derived whole continua of reactivity. The value of this approach has been demonstrated by the finding that certain lesions of the central nervous system clearly alter force curves without affecting escape thresholds (Vierck, Hamilton, and Thornby, 1971). Although per cent of escape responses reached plateau at the mid-range of intensities in the present study, other measures of response frequency appear to be sensitive indicators of pain reaction intensity. The number of "anticipatory" escape responses, *i.e.*, those made during the 1-sec delay interval when leg shock could not be terminated, appeared to increase as a function of stimulation intensity in this study (not shown), and other investigators have thoroughly demonstrated this relationship between the rate of anticipatory or elicited responses and level of shock (Appel, 1968; Cohen, 1968; Domjan and Rowell, 1969; Hutchinson, Azrin, and Renfrew, 1968; Riess, 1970).

On trials where escape of leg shock was punished by brief but intense tail shock, and withholding of escape for 8 sec permitted the animals to respond to avoid tail shock, the leg shock duration curves were elevated throughout the range of intensities delivered. Comparing free and punished escape thresholds (50% escape responses) over a block of five early testing sessions, they were 17 and 28 mA for Animal #2, and 2 and 17 mA for Monkey #3. These thresholds of 17 and 28 mA on punished escape trials indicate that, in the early testing sessions, 8 sec of leg shock in the mid-range of intensities was equated in aversiveness to tail shock that was intended to be maximally

aversive without producing tissue damage. Thus, it appeared in the early stages of testing that the paradigm was successful in producing independent escape tendencies that approximated pain detection and pain tolerance functions as defined in human experiments (Gelfand, 1964).

Because there was considerable inter-individual variability in the early data, such that the tolerance function of one animal overlapped the detection curve of another, the animals were tested repeatedly to determine the stability of the shock duration curves. Comparison of Figures 2 and 3 shows that the shock duration curves for free escape were stable over time, but those for punished escape were not. All animals developed a rigid pattern of never emitting an escape response that would be punished by tail shock. Thus, after 30 testing sessions they consistently chose 8 sec of leg shock in preference to 1 sec of leg shock followed immediately by 0.1 sec of tail shock. This finding could be explained in part by assuming that the animals resolved a conflict that was, itself, highly aversive; that is, by consistently taking leg shock for the maximum duration they avoided making a decision on each trial, involving comparison of two different aversive stimuli. But why did none of the animals adopt the solution of always escaping with minimal latency and taking the brief tail shock? It will be necessary to manipulate a number of schedule and shock parameters to answer this question.

Preliminary evidence from a similar paradigm indicates that an intense punishing shock is not necessary to induce withholding of escape responses up through 48 mA. One *Macaca speciosa* monkey has been tested on the same schedule of free escape on blue-light trials. On red-light trials, the monkey can press the lever to obtain food reinforcers if leg shock is not escaped within 8 sec. Escape of leg shock is never punished with additional shock, nor are food reinforcers available if escape responses are emitted. This animal gives detection thresholds (on blue-light trials) under 8 mA, but leg shock is seldom escaped on red-light trials. This behavior contrasts sharply with that of five *Macaca speciosa* monkeys utilized in a previous study (Vierck, *et al.*, 1971) in which the paradigm was simpler: withholding of escape responses was automatically reinforced with food (no bar response

required), and escape responses were neither reinforced with food nor punished with additional shock. The escape thresholds of these animals ranged from 6 to 13 mA, and the shock duration curves were extremely stable over months of testing. Therefore, it appears that some feature of the free *vs* punished discrimination was important to the high level of shock tolerance demonstrated by the animals in the present study. The requirement of an active bar press (in addition to passive endurance of leg shock) in order to avoid tail shock was specifically made to enhance the contrast between free and punished escape trials, and it may have been critical in this regard. Although the monkeys frequently pressed the bar during leg shock in the early sessions, they all developed the pattern of waiting for leg shock offset to press the bar and avoid tail shock. Hence, the high levels of tolerance did not appear in conjunction with an overt substitute activity (for disc pressing) that we could detect.

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Received 12 March 1971.
(Final acceptance 9 August 1972.)