

# Operant Conditioning of Primate Spinal Reflexes: The H-Reflex

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## SUMMARY AND CONCLUSIONS

1. The study of primate memory substrates, the CNS alterations which preserve conditioned responses, requires an experimental model that fulfills two criteria. First, the essential alterations must be in a technically accessible location. Second, they must persist without input from other CNS regions.

2. The spinal cord is the most technically accessible and readily isolated portion of the primate CNS. Recent work (42–48, 50) has demonstrated that the spinal stretch reflex (SSR), the initial, wholly segmental response to muscle stretch, can be operantly conditioned and suggests that this conditioning may produce persistent spinal alteration. The present study attempted similar operant conditioning of the H-reflex, the electrical analog of the SSR. The primary goals were to demonstrate that spinal reflex conditioning can occur even if the muscle spindle is removed from the reflex arc and to demonstrate conditioning in the lumbosacral cord, which is far preferable to the cervical cord for future studies of neuronal and synaptic mechanisms.

3. Nine monkeys prepared with chronic fine-wire triceps surae (gastrocnemius and soleus) electromyographic (EMG) electrodes were taught by computer to maintain a given level of background EMG activity. At random times, a voltage pulse just above M response (direct muscle response) threshold was delivered to the posterior tibial nerve via a chronically implanted silicon nerve cuff and elicited the triceps surae H-reflex. Under the control mode, reward always followed. Under the HR $\uparrow$  or HR $\downarrow$  mode, reward followed only if the absolute value of triceps surae EMG from 12 to

22 ms after the pulse (the H-reflex interval) was above (HR $\uparrow$ ) or below (HR $\downarrow$ ) a set value. Monkeys completed 3,000–6,000 trials/day over study periods of 2–3 mo.

4. Background EMG and M response amplitude remained stable throughout data collection. H-reflex amplitude remained stable under the control mode.

5. Under the HR $\uparrow$  mode (5 animals) or HR $\downarrow$  mode (4 animals), H-reflex amplitude (EMG amplitude in the H-reflex interval minus background EMG amplitude) changed appropriately over at least 6 wk. Change appeared to occur in two phases: an abrupt change within the first day, followed by slower change, which continued indefinitely. Change occurred in all three triceps surae muscles (medial and lateral gastrocnemii and soleus). Under the HR $\uparrow$  mode, H-reflex amplitude rose to an average of 213% of control, whereas under the HR $\downarrow$  mode it fell to an average of 68% of control.

6. The results demonstrate that the H-reflex can be operantly conditioned. Similarities between H-reflex and SSR conditioning suggest similar or identical mechanisms.

7. The H-reflex bypasses the muscle spindle and other sensory receptors; thus these receptors cannot be the site of the functional change in the spinal reflex arc. At present the most probable site(s) are the Ia-synapse on the  $\alpha$ -motoneuron, the  $\alpha$ -motoneuron itself, and possibly other oligosynaptic pathways from Ia, Ib, and II afferents.

8. The salient features of operantly conditioned H-reflex change, combined with related clinical and laboratory data on spinal cord plasticity, suggest that change may be due to intrinsic spinal alteration. If so, this alteration

constitutes a memory substrate that should prove accessible to physiological, anatomical, and biochemical study at the neuronal and synaptic levels with available techniques.

## INTRODUCTION

### *Study of memory substrates in higher animals*

The substrates of memory, the CNS alterations which preserve a conditioned response, do not necessarily reside in the CNS pathways that connect the stimulus to the response. A specific region may be essential for display of a conditioned response, but the region may have no role whatsoever in memory itself; the substrate that preserves the response may reside elsewhere. Thus an experiment designed to study memory substrates must fulfill two requirements (41, 43, 44). First, it must locate a CNS alteration essential to a conditioned response in a location that is technically accessible. Second, it must demonstrate that the alteration is not simply a product of activity originating elsewhere, i.e., that it persists without input from elsewhere in the CNS and therefore qualifies as a memory substrate. These criteria are difficult to satisfy in a higher vertebrate. Access and isolation are limited and normally involve extremely disruptive procedures. The only CNS region that is readily isolated, in which inputs and outputs are readily monitored, and in which major cell groups are defined and accessible, is the spinal cord.

### *Evidence that the spinal cord should be able to contain memory substrates*

While the spinal cord was a focus for earlier investigations (4, 12, 16, 22, 36), it is not at present a popular region for the study of memory. Most current efforts are directed at more rostral regions of the CNS. The cord is commonly conceived to be a stable structure, made up of fixed inflexible neuronal circuits which simply respond in stereotyped fashion to inputs from supraspinal areas and from peripheral nerves. However, extensive clinical and laboratory evidence demonstrates that the spinal cord is capable of considerable plasticity and indicates the circumstances under which such plasticity can occur. These data show that if activity in descending pathways or in sensory

afferents is altered, and if this alteration continues long enough, intrinsic changes in the spinal cord can occur, which can last beyond removal of the altered incoming activity. Impressive evidence for this spinal cord capacity was reported by DiGiorgio (10). Her work was subsequently confirmed and extended by others (see 13 and 21 for review of DiGiorgio's work and later studies). These experiments showed that the asymmetric hindlimb postures produced by hemicerebellar lesions last for weeks after thoracic cord transection if at least 45 min pass between the occurrence of the lesion and transection (i.e., if the pathological descending activity has 45 min to alter the cord). The crucial changes were shown to be in the cord itself, not in the peripheral apparatus. Comparable phenomena occur with a variety of suprasegmental lesions. A larger, more diverse body of data for cord plasticity is composed of the many clinical and experimental studies indicating that cord transection begins a series of changes in spinal cord function, which continue to develop over many months (6, 27, 28, 30, 32). Furthermore, recent studies indicate that the evolution of spinal cord reflexes that occurs during normal development is dependent on descending influences, since such evolution may fail to occur in the presence of suprasegmental lesions (31). The capacity of altered peripheral input to produce intrinsic cord changes is illustrated by the evidence that the isolated spinal cord can be classically conditioned (33) and by recent studies of flexor reflex plasticity due to thermal injury (52). These clinical and laboratory data demonstrate that, with the correct impetus over sufficient time, the spinal cord has the capacity for intrinsic and persistent change.

The evidence that chronic pathological or developmental change in descending activity can produce intrinsic spinal cord alterations suggests that chronic operantly conditioned change in descending activity might also do so. Thus, if an animal performed a task that required long-term tonic alteration in the descending activity impinging on the spinal cord, intrinsic cord changes might be expected to occur. Such changes, occurring as part of normal learning in an intact animal, would qualify by any criteria as memory substrates and would be located in a technically accessible region of the CNS.

### *Operant conditioning of the spinal stretch reflex*

Our recent studies (42–48, 50) trained monkeys on such a task. The task required that animals change the amplitude of the initial component of the muscle stretch response, the spinal stretch reflex (SSR) (17, 26), without change in background  $\alpha$ -motoneuron tone as measured by EMG or in initial muscle length. The SSR is wholly spinal and is thought to be largely monosynaptic (see 26 for review and see DISCUSSION). Because the stretch eliciting the reflex occurred at an unpredictable time, and because the SSR occurred before any other possible CNS response, this task required continual alteration of activity in descending pathways acting on the spinal arc of the reflex. This continual alteration in descending activity had to be present for the 5–7 h per day the animals worked at the task over data collection periods of several months. When animals were first confronted with the requirement to increase or decrease SSR amplitude, amplitude changed in the correct direction by  $\sim 8\%$  within 6 h. After this abrupt small phase I change, very slow phase II change of 1–2% per day occurred over subsequent weeks and months as the animal continued to work at the task. SSR amplitude eventually increased to more than 150% of control or decreased to  $\sim 50\%$ . If the requirement was reversed, amplitude change reversed, also in the same two-phase fashion. Change was relatively specific to the agonist (biceps) muscle and persisted for weeks in the absence of task performance. The most probable interpretation of these results, discussed in detail elsewhere (46), is that the immediate small phase I change represents a rapid operantly conditioned change in tonic descending activity impinging on the spinal arc of the reflex and producing the small appropriate change in SSR amplitude. The subsequent very slow phase II change, which develops over months, is most probably due to gradual plastic alterations produced by continuation of the tonic change in descending activity responsible for phase I. If such plastic changes occur in the spinal cord, they should constitute technically accessible substrates of memory.

### *The present study*

The studies discussed above (42–48, 50) suggest that spinal reflex conditioning may

create intrinsic spinal cord alterations. However, they leave open several other possibilities. First, the site of the functional change in the reflex arc could be the peripheral sensory apparatus, the muscle spindle. Second, while the functional change might occur in the cord, the persistent alteration maintaining the functional change might be entirely supraspinal. By demonstrating operant conditioning of the H-reflex, the electrical analog of the SSR, the present study sought to eliminate the first possibility and to provide the means for later studies to eliminate the second.

As illustrated in Fig. 1, the H-reflex (5) is elicited from a muscle, such as the soleus or gastrocnemius, by delivering a minimal electrical stimulus to the muscle's nerve. This minimal stimulus excites only the largest axons, group I sensory fibers and the largest motoneuron axons. Motor axon excitation proceeds to the muscle and produces the direct muscle response, or M response. Ia-fiber excitation proceeds centrally and excites the  $\alpha$ -motoneuron monosynaptically, producing the H-reflex in the muscle. While other large afferents (i.e., Ib) and oligosynaptic paths may play some role (see DISCUSSION), the arc of the H-reflex does not include the muscle spindle or any other sensory receptor. Thus if H-reflex conditioning occurred, it could not be ascribed to change in sensory organ response to the stimulus eliciting the reflex.

H-reflex conditioning required modification of the experimental design. The earlier SSR studies described conditioning in upper arm muscles. However, it was preferable to attempt H-reflex conditioning in the leg, specifically in the triceps surae (soleus and medial and lateral gastrocnemii). The H-reflex is most prominent in these muscles. In addition, the relatively short peripheral pathway serving the monkey arm muscles would have made it extremely difficult to differentiate reliably the M response (the direct muscle response) from the H-reflex on the basis of latency.

H-reflex conditioning in the lower limb not only eliminates the sensory organs as the site of functional change in the reflex arc. It prepares the way for study of the second possibility, exclusively supraspinal alteration. Demonstration of persistent spinal alterations (i.e., spinal memory substrates) will require acute studies in anesthetized conditioned animals before and after spinal cord transection

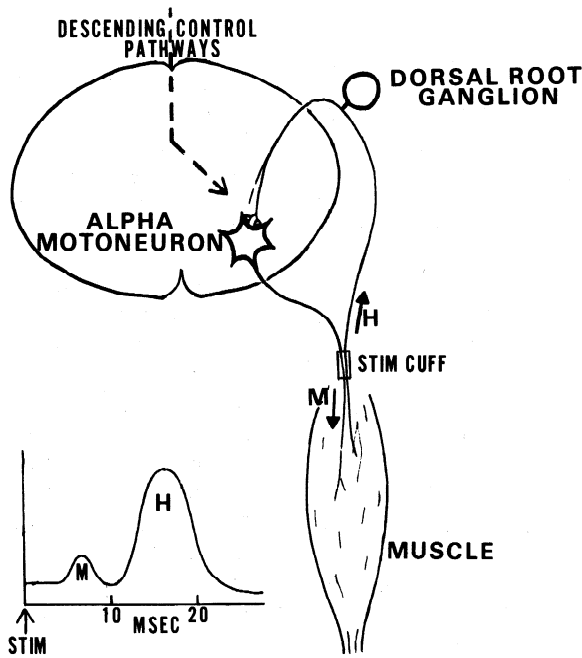


FIG. 1. The H-reflex arc. The inset illustrates M response (direct muscle response) and H-reflex as seen in triceps surae EMG.

(i.e., after removal of all descending input). Such studies are much less difficult in the lumbosacral cord.

Thus this study's goals were to determine whether spinal reflex conditioning requires participation of the peripheral sensory receptors in the reflex arc and to prepare for future studies of possible persistent alterations in the spinal cord.

#### METHODS

Experimental design and techniques were adapted from those used in earlier studies of SSR operant conditioning (44).

##### *Animal preparation and environment*

Nine monkeys (*Macaca nemestrina*, male, 6–10 kg) were placed under general anesthesia and implanted with chronic stimulating and recording electrodes. To elicit the H-reflex from triceps surae [medial gastrocnemius (MG), lateral gastrocnemius (LG), and soleus (SOL) muscles] a silicon rubber cuff with embedded stainless steel fine-wire electrodes was placed around the posterior tibial nerve just above the knee (37, 38). (This cuff of necessity also stimulated fibers serving more distal foot and toe plantar flexors.) To record EMG activity, stainless steel fine-wire electrodes (3) were inserted in MG, LG, and SOL and their antagonist tibialis an-

terior (TA) using previously described techniques (44). These electrodes were about 1.5 cm long and were spaced widely in the muscle so that their data would be as representative as possible. (In addition, to record hemispheric responses to the tibial nerve stimulus, a small stainless steel screw was placed epidurally in the skull in the midline over the leg region of primary somatosensory cortex. A reference screw electrode was placed in the frontal sinus. Data from these electrodes will be covered in a subsequent report.) The Teflon-coated wires from all three types of electrodes passed subcutaneously to a common exit either near one elbow (6 animals) or on the dorsum of the foot (3 animals) and were attached to a small connector plug.

During data collection, animals remained in the laboratory continuously. This design allowed continual data collection and ensured that the implanted leg was almost totally devoted to the task described below. As previously discussed (44), such chronic uniform exposure to the task appears important for the production of long-term operant changes and for the proper analysis of other sources of variation (45, 49).

The lab accommodated six monkeys simultaneously, in three 2 m × 1 m frames. In each frame, two monkeys faced each other, 1 m apart. Each was held by a loosely fitting Plexiglas neck collar and sat on a 1 m<sup>2</sup>, smooth, flexible grid. For six of the nine animals, legs and arms were free, except that

movement of the arm from which the electrodes exited was partially limited just below the shoulder to protect the connector. For the other three animals, in which the electrodes exited from the dorsum of one foot, the foot rested in a custom-made cast with ankle at an angle of  $\sim 90^\circ$  (very much as if the animal's foot were on a car accelerator pedal). Both arms and the other leg were free. All animals were able to assume a variety of natural waking and sleeping postures (18). Lab lighting, controlled by a timer, was sharply reduced for 9 h, usually from 2100 to 0600. Monkeys ate standard chow from food dishes replenished four times per day and received fresh fruit at least once per day. Daily fluid intake (composed of earned rewards and daily supplements) satisfied established requirements (11). Each animal received repeated and meticulous total body inspections. Occasional incipient abrasions received immediate appropriate treatment. Animals remained active, free of significant abrasions, and in good health throughout the study.

### Equipment

EMG from the electrodes in MG, LG, SOL, and TA was differentially amplified ( $\times 1,000$ , bandpass 10–2,000 Hz), and then digitized by a DEC 11/34 minicomputer system, which interfaced with all six monkeys simultaneously and continuously under the program ELIZAN (by Mega, Fairfax, VA). The computer recorded the absolute value of each muscle's digitized EMG (equivalent to full-wave rectification). It controlled the four outputs visible in Fig. 2A: 1) the large upper light, which simply indicated that the system was running, 2) the large lower light, which indicated that background EMG was in the proper range (see below), 3) the tibial nerve stimulus at M response threshold and the simultaneous flash of the small round light, and 4) the brief reward squirt from the syringe-solenoid system mounted 0.5 m in front of and above the monkey.

### Task

Via its four EMG inputs and four digital outputs per monkey ("system on" light, "correct background EMG" light, nerve cuff stimulus and accompanying small round light, and reward pulse), the computer monitored and controlled the task illustrated in Fig. 2B. It continually updated a 250-ms running average of the absolute value of EMG from one of the triceps surae electrode pairs (usually LG or SOL). If this running average entered a preset range, the computer lit the large lower light. If the average remained correct for a randomly varying 1.2- to 1.8-s period the computer delivered a brief (100  $\mu$ s) capacity coupled voltage pulse at M response threshold to the tibial nerve via the nerve cuff.

This stimulus elicited a threshold M response and a larger H-reflex from LG, MG, and SOL. The M response was evident in the EMG at 3–9 ms and the H-reflex at  $\sim 12$ –22 ms. The computer digitized EMG from all muscles following the nerve cuff stimulus. It divided the 50 ms following the stimulus into a series of windows (usually 25 windows: 10 of 1 ms, followed by 10 of 2 ms, followed by 5 of 4 ms) and calculated the average absolute value of EMG within each window. (Thus, with the computer digitizing each EMG channel at 2,000 Hz, two absolute values were averaged to determine EMG amplitude for a 1-ms window, 4 values for a 2-ms window, and 8 values for a 4-ms window.) The computer gave a reward squirt 0.2 s after the stimulus.

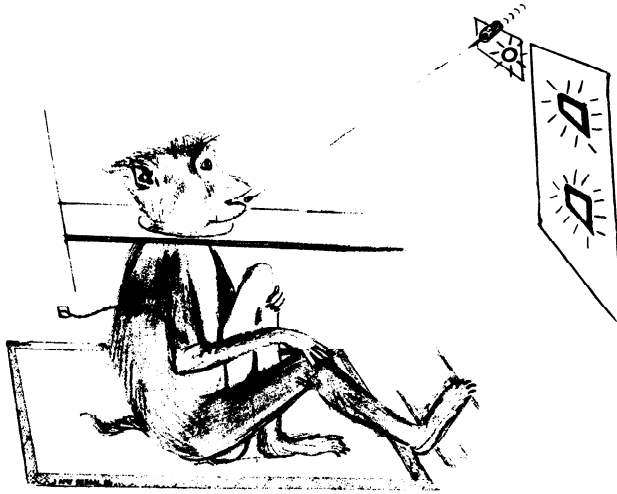
Because the stimulus was at M response threshold and thus barely perceptible to the animal, the computer flashed the small round light next to the squirter at the time of the stimulus. This visual signal, far too late to have any effect on the H-reflex, gave the animal time to open its mouth for the reward squirt occurring 0.2 s later.

Finally, the computer calculated the average absolute amplitude of EMG for the M response interval (3–9 ms after the stimulus). If this value was above a preset target, the computer reduced the size of the stimulus for the next trial by a set amount; if it was below, the computer increased the stimulus size for the next trial by the same amount. This trial-by-trial adjustment of stimulus amplitude ensured that the stimulus stayed near M response threshold in spite of any acute or chronic changes in nerve cuff position, performance, or other factors.

Thus, in a quite stereotyped manner, the monkey achieved proper triceps surae background EMG, maintained it for a random period, received the nerve cuff stimulus and saw the small round light flash, opened its mouth, and received the reward squirt. The animal was trained on this simple task by standard operant techniques. Initially the EMG running average limits were very wide, so that the animal often satisfied them spontaneously. As it began to satisfy the limits more frequently, the limits were gradually raised and tightened until a level was reached that was associated with a substantial H-reflex on cuff stimulation. Once trained, animals typically completed 10–15 trials per min and worked 5–7 h per day. Thus each performed 3,000–6,000 trials per day. Animals worked most intensively during the day, when the lab lights were bright (0600–2100), but did perform substantial numbers of trials during the night, when the lights were dim (2100–0600) (45, 49).

As shown in Fig. 2B, this task operated under any one of three modes. In the control mode, all trials were rewarded. The monkey simply maintained the correct background EMG level, received the stimulus, and was rewarded. In the HR $\uparrow$  or HR $\downarrow$

A



## B TWO-PART TASK

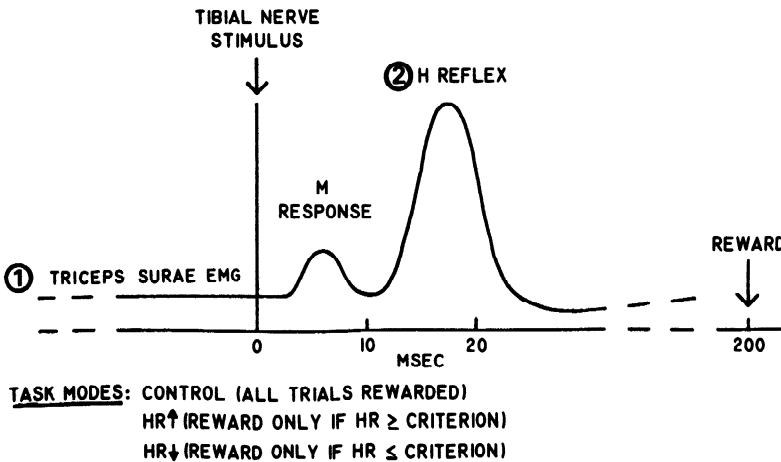


FIG. 2. Experimental design. *A*: animal performing task. Implanted fine-wire triceps surae EMG electrodes and tibial nerve cuff stimulating electrodes exit at posterior arm. *Large upper light* indicates system is on. *Large lower light* indicates correct triceps surae background EMG. *Small round light* flashes with delivery of nerve cuff stimulus. Solenoid-powered syringe delivers reward squirt. *B*: task performed by animal. The animal keeps triceps surae background EMG within a preset range for a randomly varying 1.2- to 1.8-s period. At the end of this period the nerve cuff stimulus elicits a threshold M response and an H-reflex. Under the control mode, a reward squirt always occurs 0.2 s following the stimulus. Under the HR↑ or HR↓ mode, reward occurs only if triceps surae EMG amplitude in the H-reflex interval (usually 12–22 ms after the stimulus) is above (HR↑) or below (HR↓) a criterion value.

mode, reward occurred only if triceps surae EMG amplitude in the H-reflex interval (typically defined as 12–22 ms after the stimulus) was above (HR↑) or below (HR↓) a criterion value. On initiation of the HR↑ or HR↓ mode, the criterion value was chosen on the basis of the control mode data so as to reward about 50% of the trials. As H-reflex amplitude changed in subsequent days and weeks, and reward percentage consequently increased, the cri-

terion value was periodically changed to reduce reward percentage back toward 50% and thus maintain the impetus for H-reflex change.

### Data

For each monkey the computer provided a data summary every 3 h and a grand summary every 24 h (Fig. 3). Each summary included number of trials, number of rewards, and average absolute value of

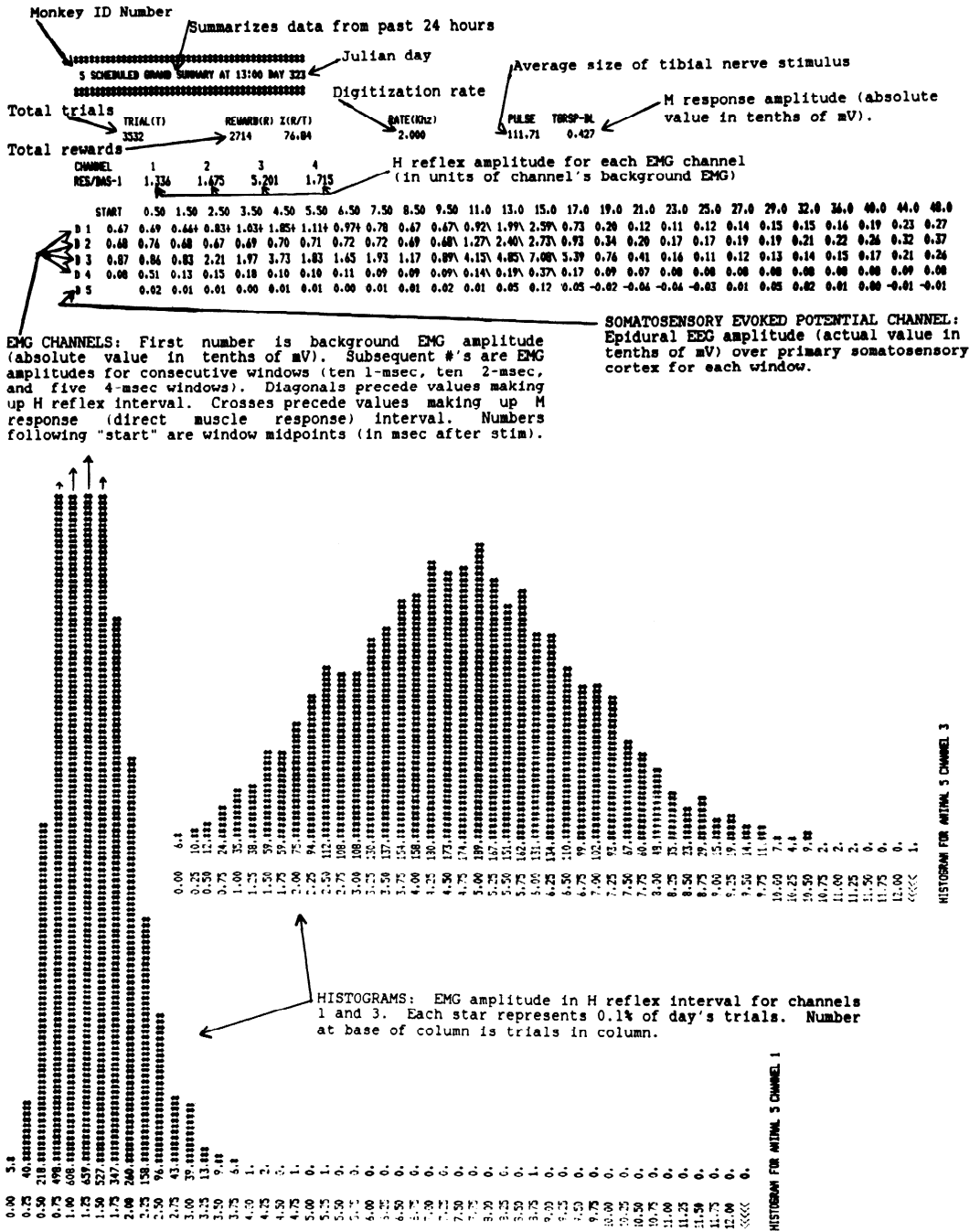


FIG. 3. Sample grand summary of 24-h data from one monkey. The computer provides such a grand summary for every animal every day. It also gives 3-h summaries throughout the day. See text for full explanations of terms.

each muscle's EMG for the 50 ms prior to the stimulus and for each 1-, 2-, or 4-ms poststimulus window out to 50 ms after the stimulus. It gave each muscle's average H-reflex amplitude (calculated as

average EMG amplitude in the H-reflex interval minus average background EMG amplitude and presented in units of average background EMG amplitude). It also gave average M response am-

plitude of the muscle used to control stimulus pulse amplitude (calculated as average EMG amplitude in the M response interval minus average background EMG amplitude and expressed in tenths of millivolts). Finally, it provided histograms of H-reflex interval EMG amplitudes for all the day's trials. Figure 3 shows a typical grand summary. In addition, analog recordings of series of several hundred trials were made periodically on an instrumentation tape recorder. These recordings aided monitoring of system calibration and furnished raw EMG data from single trials for examination and illustration. It is important to stress that all EMG measurements by the computer were absolute value. This measurement is equivalent to that obtained by full-wave rectification.

#### *Data collection and animal performance*

Data were obtained from each animal for 2–3 mo. Since background EMG, M response amplitude, and H-reflex amplitude depended on the electrode pair, the same pairs were used throughout data collection. Each animal worked initially under the control mode for 10–25 days and then under the HR $\uparrow$  or HR $\downarrow$  mode for 40–85 days. Assignment to HR $\uparrow$  or HR $\downarrow$  mode was determined prior to the control mode exposure and thus did not depend on control H-reflex amplitude. In general, assignment was alternated from one animal to the next, in order to provide comparable numbers of HR $\uparrow$  and HR $\downarrow$  animals. For the first five animals, reward was based on H-reflex amplitude from one muscle (usually LG), though synergist H-reflexes were often monitored. For the last four animals, reward depended on all three (LG, MG, SOL) H-reflex amplitudes simultaneously. Each muscle's H-reflex had to satisfy its own criterion value.

Throughout data collection from each animal, we noted no significant changes in general posture, limb position, daily performance schedule, or other aspects of animal behavior. The six animals for which the implanted leg was free each adopted a standard working position for the leg early in training and kept it unchanged throughout data collection. Several extended the leg nearly horizontally in front, with the foot pressing against some part of the frame. This leg position was comparable to that of the three animals with foot-ankle casts (i.e., as if the foot were on an accelerator pedal). Others remained in a full crouch, both legs flexed, while working. Thus, in all animals, ankle, knee, and hip angles during task performance showed no visible change over the data collection period. Several animals often lightly scratched one leg or the other while working at the task. This behavior was erratic and did not change with task mode. In the three animals with casts, a 5–10% decrease in calf circumference and a  $\sim 10^\circ$  decrease at each extreme of ankle and knee movement occurred in the im-

planted leg. These changes were not related to task mode. They were attributed to decreased mobility and use.

## RESULTS

### *Control data*

Triceps surae background EMG varied from 40 to 100  $\mu\text{V}$  absolute value depending on the electrode pair (equivalent to the rms value of a sine wave of 120–300  $\mu\text{V}$  peak-to-peak amplitude). Antagonist (TA) background EMG was minimal, typically averaging  $< 10 \mu\text{V}$  absolute value, some of which may have been far-field pickup from triceps surae. For each monkey, the computer maintained M response amplitude (EMG amplitude in the M response interval minus background EMG amplitude) near a target value that was usually  $\sim 50\%$  of background EMG amplitude. Depending on the monkey, the muscle, the EMG electrode pair, and doubtless also on the M response target value and the stimulating electrode pair, H-reflex amplitude (EMG amplitude in the H-reflex interval minus background EMG amplitude) varied from 0.4 to 7.8 times background EMG amplitude. In the preliminary training period, prior to data collection, the required background EMG and the M response target value were varied over a considerable range. On the basis of this evaluation, the required background EMG range and the M response target value for the data collection period were chosen so as to maximize H-reflex amplitudes.

For each monkey, background EMG, M response latency and amplitude, and H-reflex latency and amplitude were stable throughout the 10- to 25-day control period, the first part of the data collection period. Figure 4 shows daily average amplitudes for background EMG, H-reflex, M response, and stimulus pulse for one monkey over a 25-day control period. Comparably stable control mode data were obtained from each animal before imposition of the HR $\uparrow$  or HR $\downarrow$  mode. For all animals, the standard deviation of daily average amplitudes averaged 5% for background EMG and 15% for the M response and the H-reflex. The daily average stimulus pulse amplitude was also quite stable, with an average standard deviation of 3%. (This was somewhat unexpected, since it was anticipated that slight shifts in cuff position, progressive connective



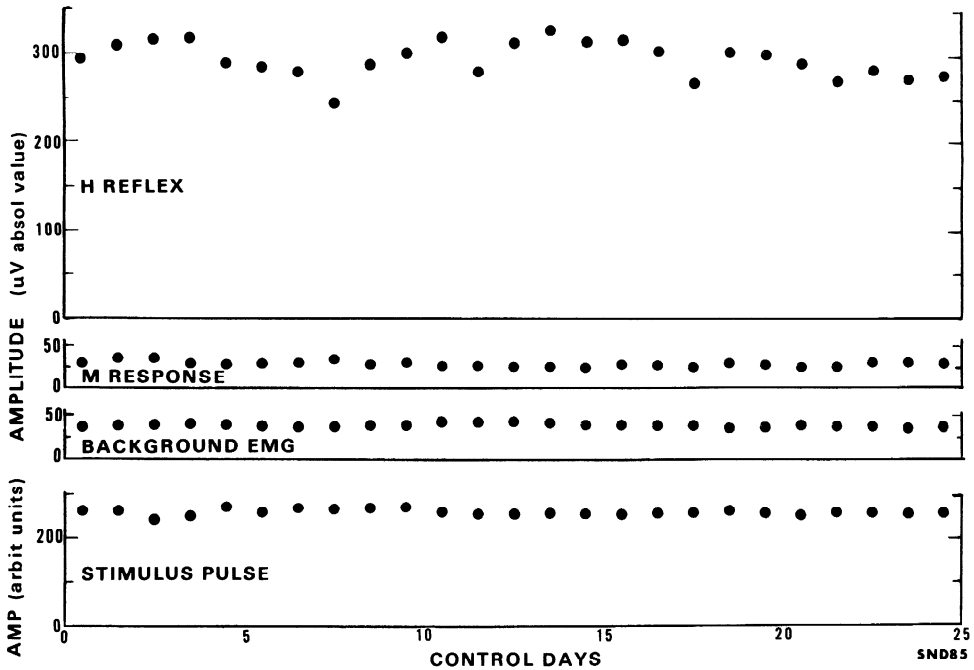


FIG. 4. Daily average H-reflex, M response, background EMG, and stimulus pulse amplitudes over one monkey's 25-day control mode exposure. All 4 measures remain stable over the prolonged control period.

tissue investment, etc., would often produce significant acute or chronic changes in the stimulus strength necessary to maintain the target M response.)

#### HR↑ mode

After collection of control data for a 10- to 25-day control mode exposure, five monkeys were switched to the HR↑ mode for a 40- to 85-day period. Background EMG and M response amplitudes remained stable. In contrast, H-reflex amplitude increased to 213% ( $\pm 73\%$  SE) of control H-reflex amplitude. Modest change was normally evident in the first few days and increase continued over weeks. The magnitude of change varied considerably from monkey to monkey, and from muscle to muscle in those animals in which multiple muscles were trained. For the five monkeys, average H-reflex amplitudes for the final 10 days of HR↑ mode exposure were 457, 247, 130, 123, and 110% of control H-reflex amplitude. Thus two animals showed great increases, two showed moderate increases, and one showed a minimal increase. The *t* test (35), used to compare H-reflex amplitudes for the final 10 HR↑ days with control H-reflex am-

plitude, gave  $P \ll 0.001$  for each of the first three increases,  $P < 0.001$  for the fourth, and  $P > 0.05$  for the fifth. The magnitude of increase was not correlated with control H-reflex amplitude. Thus the greatest increases were not always shown by H-reflexes with the smallest control mode amplitudes. The first and third values are from animals in which all three muscles (LG, MG, SOL) were simultaneously conditioned, and thus are averages for the muscles trained.

Figure 5 shows representative data. Figure 5A displays average H-reflex amplitude from one monkey for each 5-day period for 40 days following HR↑ mode onset, in terms of control mode H-reflex amplitude. H-reflex increase takes place over weeks. Average background EMG, also shown, remains near its control mode level, indicated by the lower dashed line. Figure 5B shows histograms from a monkey before and after prolonged HR↑ exposure. Each shows the distribution of single-trial H-reflex interval amplitudes for a full day ( $>3,000$  trials). The distribution for the HR↑ day is well to the right of that for the control day. Finally, Fig. 5C shows poststimulus EMG under the control and HR↑ modes. The top

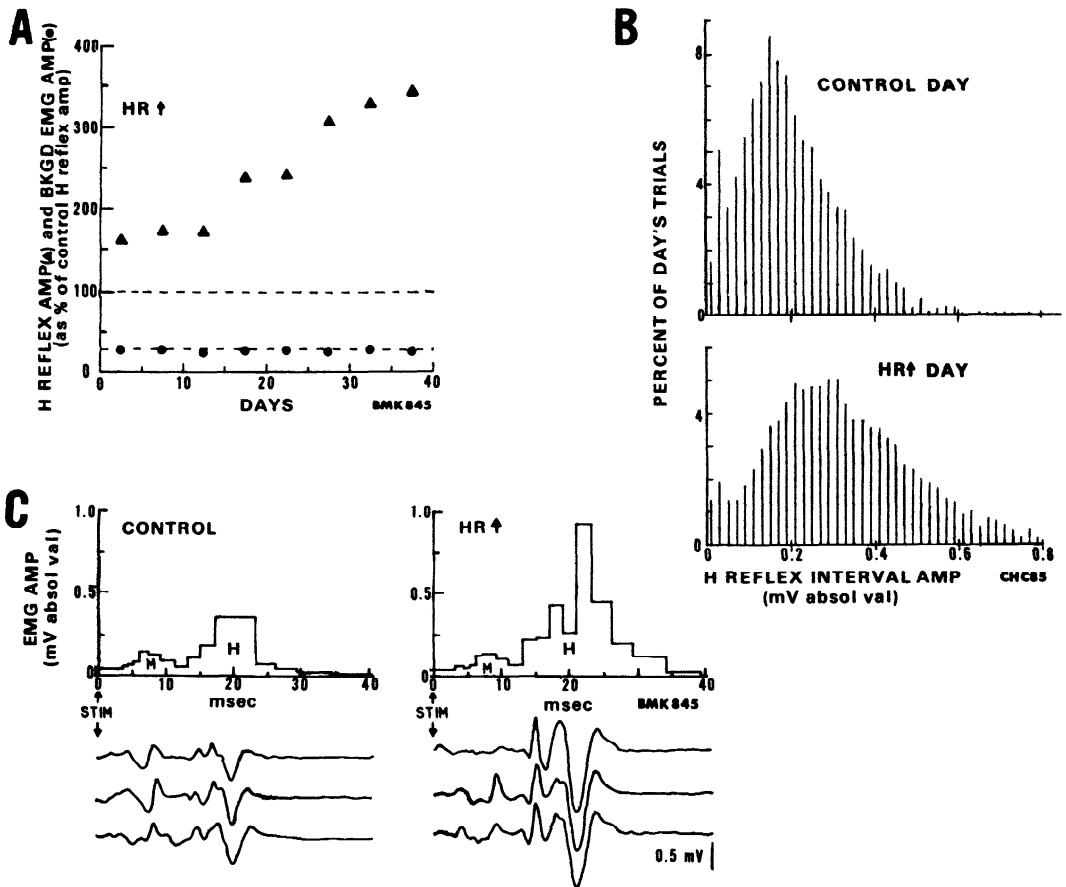


FIG. 5. *A*: 5-day average H-reflex amplitudes (filled triangles) and background EMG (filled circles) from a monkey following beginning of HR $\uparrow$  mode exposure (as % of control mode H-reflex amplitude). Under the HR $\uparrow$  mode, H-reflex amplitude rises gradually over weeks. Background EMG remains near its control mode level, indicated by the lower dashed line. *B*: distribution of H-reflex interval amplitudes for a day (>3,000 trials) under the control mode (top) and for a day following prolonged HR $\uparrow$  exposure (bottom). Note the marked right shift in distribution of H-reflex amplitudes after HR $\uparrow$  exposure. *C*: poststimulus EMG from one monkey under the control mode and after prolonged HR $\uparrow$  mode exposure. The top trace is average absolute value of poststimulus EMG for a full day (>3,000 trials). The lower traces are raw EMG from single trials. Background EMG, shown by time 0 value in the top trace, and M response are the same for both days. The H-reflex is much larger after HR $\uparrow$  exposure.

trace on each side is average absolute value of poststimulus EMG for a full day (>3,000 trials); the lower traces are raw EMG from single trials. Background EMG (indicated by the top trace's time 0 value) and the M response are the same for both days. In contrast, H-reflex amplitude is much greater after prolonged HR $\uparrow$  mode exposure.

#### HR $\downarrow$ mode

After control mode exposure, four animals were switched to the HR $\downarrow$  mode for 40–67 days. Background EMG and M response amplitude remained stable. H-reflex amplitude

decreased to an average of 68% ( $\pm 5\%$  SE) of control H-reflex amplitude. As with H-reflex increase, decrease occurred over weeks. For the four monkeys, average H-reflex amplitudes for the final 10 days of HR $\downarrow$  exposure were 62, 62, 69, and 79% of control H-reflex amplitude. The *t* test (35), used to compare H-reflex amplitudes for the final 10 HR $\downarrow$  days with control H-reflex amplitude, gave  $P \ll 0.001$  for each of the first three decreases and  $P = 0.05$  for the fourth. The third and fourth values are from animals in which three muscles were simultaneously conditioned and thus are averages.

Figure 6 displays representative data. Figure 6A shows average H-reflex amplitude from one monkey for each 5-day period for 40 days following HR↓ mode onset in terms of control mode H-reflex amplitude. H-reflex decrease occurs gradually. Average background EMG, also shown, remains near its control mode level, indicated by the lower dashed line. Figure 6B gives histograms from a monkey before and after prolonged HR↓ exposure. Each shows the distribution of single-trial H-reflex amplitudes for a full day (>3,000 trials). The marked shift to the left in the lower histogram indicates a substantial fall in H-reflex amplitude under the HR↓ mode. Figure 6C displays poststimulus EMG under control and HR↓ modes. Daily average absolute value traces

(>3,000 trials) and raw single-trial traces are shown. Background EMG (shown by the top trace's *time 0* level) and M response are stable, whereas H-reflex amplitude is much reduced under the HR↓ mode.

#### Evidence for a two-phase process

Earlier work indicated that SSR amplitude change occurred in two phases (46). An initial 8% phase I change occurred within 6 h of SSR↑ or SSR↓ mode onset. Subsequent, much slower phase II change occurred at a rate of 1–2% per day for at least 2 mo. While the present H-reflex data are limited, they also suggest a two-phase process. Figure 7, combining data from all monkeys, shows average daily change in the required direction in each of the first 5

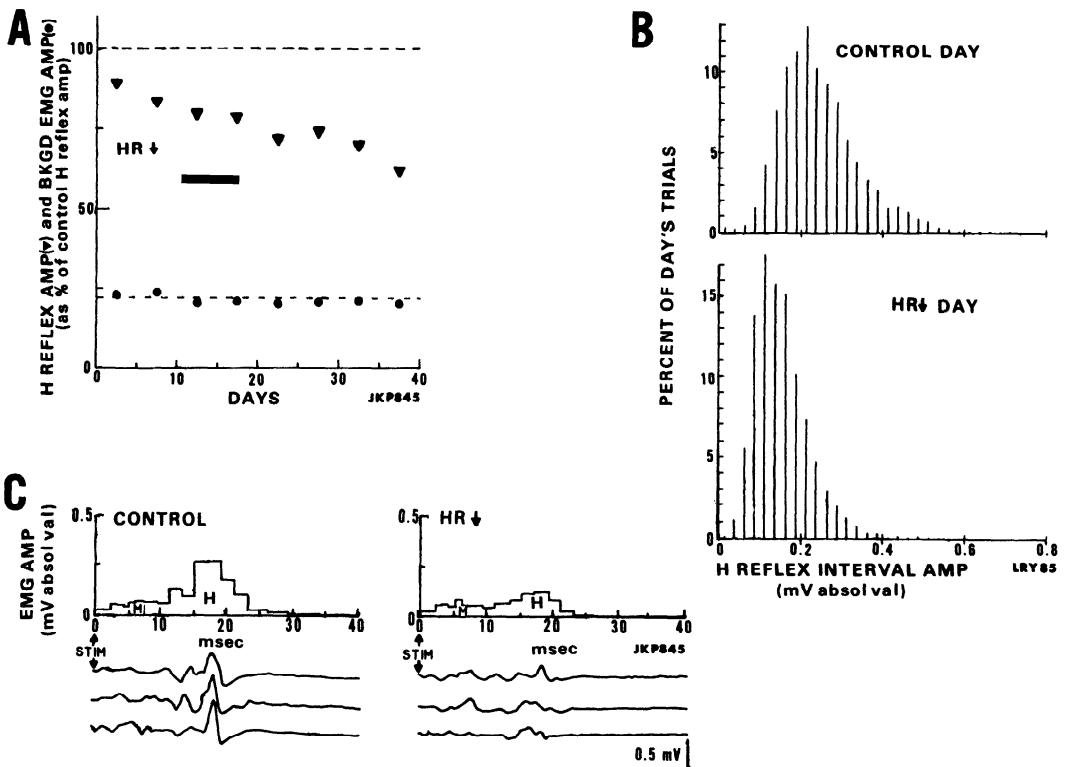


FIG. 6. A: 5-day average H-reflex amplitudes (filled triangles) and background EMG (filled circles) from a monkey following beginning of HR↓ mode exposure (as % of control mode H-reflex amplitude). Under the HR↓ mode, H-reflex amplitude falls gradually over weeks. Background EMG remains near its control mode level, indicated by the lower dashed line. B: distribution of H-reflex interval amplitudes for a day (>3,000 trials) under the control mode (top) and for a day following prolonged HR↓ exposure (bottom). Note the marked left shift in distribution of H-reflex amplitudes after HR↓ exposure. C: poststimulus EMG from one monkey under the control mode and after prolonged HR↓ mode exposure. The top trace is average absolute value of poststimulus EMG for a full day (>3,000 trials). The lower traces are raw EMG from single trials. Background EMG, shown by the *time 0* value in the top trace, and M response are the same for both days. The H-reflex is much smaller after HR↓ exposure.

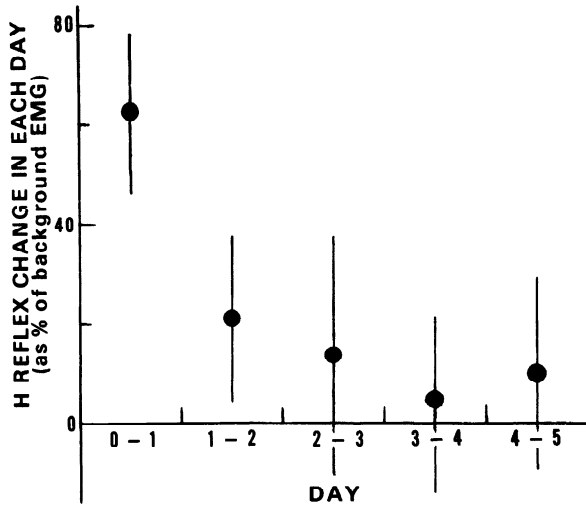


FIG. 7. Data from all animals combined to show average daily H-reflex change ( $\pm$ SE) in required direction in each of the first 5 days after HR $\uparrow$  or HR $\downarrow$  onset. H-reflex change is expressed in percent of background EMG level, which remained stable. (For HR $\downarrow$  animals, each day's change was multiplied by  $-1$  so that HR $\uparrow$  and HR $\downarrow$  data could be combined.) Much greater H-reflex change occurs in the first 24 h then in each subsequent day.

days of HR $\uparrow$  or HR $\downarrow$  exposure. A large change occurs over the first 24 h. Subsequent days show much smaller changes (which, though barely apparent on a day-to-day basis, continue for weeks and are eventually responsible for most of the conditioned change). More data are needed for detailed plotting of the prolonged course of H-reflex change and for separate delineation of the HR $\uparrow$  and HR $\downarrow$  courses. [While the two modes show comparable 1st-day change, they probably differ somewhat in their rates of subsequent slow phase II change (46)]. Nevertheless, the available data are clearly consistent with a two-phase process.

## DISCUSSION

The results demonstrate that monkeys can change triceps surae H-reflex amplitude without change in background  $\alpha$ -motoneuron tone, as measured by EMG. H-reflex change occurred without change in the peripheral nerve excitation produced by the electrical stimulus, as measured by the corresponding M response, without noticeable change in leg posture, daily performance schedule, or overt animal behavior, and without change in H-reflex latency. On the average, the H-reflex

doubled under the HR $\uparrow$  mode and decreased by about one-third under the HR $\downarrow$  mode. The stability of H-reflex amplitude under the control mode and the fact that change under the HR $\uparrow$  or HR $\downarrow$  mode was mode appropriate indicate that H-reflex change was a specific adaptive response to a specific external condition.

H-reflex change is readily understood as an operantly conditioned phenomenon. Under the control mode, the animal maintains background EMG and is rewarded at unpredictable times (i.e., 0.2 s following H-reflex elicitation, which occurs at the end of an unpredictable interval). Under the HR $\uparrow$  or HR $\downarrow$  mode, reward still occurs at unpredictable times, but its frequency is dependent on the ongoing tonic activity in descending pathways controlling the spinal arc of the H-reflex. Proper setting of these pathways will increase the probability that reward will follow H-reflex elicitation. Because the stimulus occurs at unpredictable times and because the H-reflex occurs before any other possible CNS response, the animal can only increase reward frequency by being prepared ahead of time, by controlling the tonic descending activity so as to maintain the spinal arc of the H-reflex in the proper state.

H-reflex plasticity is almost certainly not unique to experiments such as this one. Long-term adaptive changes in the reflex arc underlying the H-reflex appear to occur in the course of normal development and in response to demands of various kinds. Spinal stretch reflexes change over the first few years of life, apparently under the control of descending pathways, since change may fail to occur in the presence of chronic supraspinal lesions (31). There is evidence that prolonged athletic training, such as that undergone by professional ballet dancers, may reduce stretch reflexes and H-reflexes (15). [Since the dominant effect of supraspinal control is to reduce spinal reflexes, this phenomenon could be interpreted as increased encephalization of the lower limbs, consistent with the very precise control necessary in dancing (48).]

This demonstration of H-reflex operant conditioning raises at least four important issues. First, is this essentially the same phenomenon as SSR operant conditioning (42–48, 50)? Second, where is the functional change responsible for H-reflex amplitude change? That is, where in the spinal arc of the reflex does function change? Third, what supraspinal structures and what descending pathways are responsible for the altered tonic input to the cord? Fourth, does H-reflex conditioning involve persistent spinal change? That is, are memory substrates present at the spinal level, and, if so, what are the substrates?

#### *Similarity to SSR operant conditioning*

Until the mechanisms of H-reflex and SSR conditioning are defined, it will not be possible to decide whether SSR and H-reflex conditioning are examples of the same phenomenon. However, their considerable similarity strongly suggests that they are.

The tasks producing the two are comparable. The H-reflex task is essentially a reduced form of the SSR task. Both make the essential demand that background EMG remain stable and thus both control the overall tone of the  $\alpha$ -motoneuron population. The SSR task also requires maintenance of a specific muscle length, in order to control for the effects of initial muscle length on spindle sensitivity and on the implanted EMG electrode pairs' measurements of muscle activity. The H-reflex task bypasses the spindle and has the M response

as a check on electrode function and thus does not need rigid control of muscle length. (Furthermore, as previously mentioned, observation of animals throughout data collection revealed no changes in limb position and thus in muscle length after imposition of the HR $\uparrow$  or HR $\downarrow$  mode.)

The course of H-reflex change is very similar to that found for SSR change (44, 46). Both progress gradually over at least 6 wk. Furthermore, SSR change and probably H-reflex change occur in two phases. Both show an almost immediate small change followed by prolonged slow change. In regard to final change achieved, HR $\downarrow$  and SSR $\downarrow$  modes are comparable, both reduce amplitude to 50–70% of control. The change produced by the HR $\uparrow$  and SSR $\uparrow$  modes varies considerably from animal to animal. The HR $\uparrow$  mode appears capable of greater changes. The greatest SSR increase in 11 attempts was 97%, whereas in the present study of 5 HR $\uparrow$  courses, one animal's H-reflex increase was 357% and another's was 147%. This quantitative difference might easily be due to arm vs. leg or SSR vs. H-reflex differences and thus does not necessarily indicate differences in the mechanisms underlying SSR and H-reflex change. Comparison of SSR and H-reflex change in terms of persistence and reversibility requires more H-reflex data (though the small amount of data available suggest similarity).

In sum, H-reflex and SSR operant conditioning are similar in task, phases of development, rates of development, and final magnitudes. At present, there is little reason to doubt that the two are different examples of the same phenomenon and share the same underlying mechanisms.

#### *Location of the functional change in the spinal arc of the H-reflex*

While change in tonic descending activity motivated by the reward contingency presumably initiates H-reflex change, it is clear that in order to change H-reflex amplitude, this activity must alter function somewhere in the spinal arc of the reflex. The peripheral sensory apparatus, specifically the muscle spindle, which is part of the SSR arc, is bypassed by the direct nerve stimulation eliciting the H-reflex. The excitation produced by this electrical stimulus was stable throughout data col-

lection as measured by the M response. Thus change in sensory receptor response to the stimulus eliciting the reflex, while it might account for SSR conditioning, cannot account for H-reflex conditioning. [It should be noted that, although the muscle spindle is not part of the H-reflex arc, it might still contribute to H-reflex change through alteration in spindle background activity. Such alteration could affect  $\alpha$ -motoneuron background state and thereby alter response to afferent input (see below).]

The remaining possible locations are three: the monosynaptic Ia afferent path to the  $\alpha$ -motoneuron, specifically the Ia-synapse on the  $\alpha$ -motoneuron; other oligosynaptic pathways to the  $\alpha$ -motoneuron, beginning with Ia, Ib, and/or large II afferents; and the  $\alpha$ -motoneuron itself.

The monosynaptic Ia [and II (39)] synapse on the  $\alpha$ -motoneuron is thought to be largely if not wholly responsible for the H-reflex and for the SSR as well (see 26 for review and see below). This synapse is subject to presynaptic inhibition, which may originate supraspinally or peripherally (2, 9, 23). Increased presynaptic inhibition is almost certainly responsible for vibratory inhibition of the H-reflex (1). Increase could also be the cause of H-reflex reduction by the HR $\downarrow$  mode, and decrease could account for the effect of the HR $\uparrow$  mode. The lack of visible change in limb position or behavior suggests that such changes in presynaptic inhibition, if they occur, are due to supraspinal rather than peripheral inputs.

The possibility that routes other than the monosynaptic Ia pathway might contribute to the SSR and even to the H-reflex has been evaluated recently by Burke et al. (7). Their results indicate that the disynaptic Ib path, and oligosynaptic Ia and II paths, could conceivably contribute to the H-reflex. One consideration renders such polysynaptic pathways somewhat less likely as the major site of functional change in the present study and suggests that the Ia monosynaptic path plays the major role. Conditioned change is uniform throughout the usual 12- to 22-ms H-reflex interval and there is no broadening or narrowing of the response with increase or decrease. Thus the earliest part of the H-reflex, which is presumably most monosynaptic, changes as much as later parts; and, when amplitude in-

creases, the response does not begin to extend well beyond 22 ms, as might be expected if polysynaptic pathways were responsible. Nevertheless, spinal pathways other than the monosynaptic Ia path remain a possible site for the functional change responsible for H-reflex conditioning.

The  $\alpha$ -motoneuron is the third possible site of functional change. Several mechanisms are conceivable. Focal postsynaptic changes in dendritic geometry or membrane properties might change motoneuron response to afferent input without affecting other aspects of motoneuron behavior (19, 34, 51). Change in the particular balance of tonic excitatory and inhibitory inputs underlying maintenance of the required background EMG might also alter the response to afferent input. Tonic inputs originating centrally (for example, in motor cortex) and/or peripherally (for example, in muscle spindles) might change. Such change in tonic inputs could alter membrane resistance, and thus the amplitude of the composite Ia EPSP, without change in background EMG. Change in  $\alpha$ -motoneuron recruitment order could modify the motoneuron population responsible for the background EMG and thus change the segment of the population closest to threshold and most susceptible to afferent input (8, 17). This altered population of susceptible cells might be more (HR $\uparrow$ ) or less (HR $\downarrow$ ) likely to fire in response to afferent excitation. Finally, antidromic conduction by the motoneuron axons responsible for the M response could excite Renshaw cells (2). Since inhibitory input from these cells could reach homonymous motoneurons just before the sensory afferent input, change in Renshaw cell function could conceivably alter motoneuron response to afferent input and thus change the H-reflex. However, as explained in the METHODS and illustrated in Figs. 5C and 6C, the stimulus was kept at M response threshold, so that M responses were very small, or, for many trials, nonexistent. Thus Renshaw cell excitation was probably minimal or absent. Furthermore, the histogram (such as Figs. 5B and 6B) did not show the bimodal distribution that would be expected if the presence or absence of an M response (and resulting Renshaw cell excitation) was a crucial factor in determining the size of the H-reflex. In addition, H-reflex amplitude under control, HR $\uparrow$ , or HR $\downarrow$  mode

was relatively insensitive to moderate changes in M response amplitude. Future work will investigate the  $\alpha$ -motoneuron's role in H-reflex conditioning by measurement of motoneuron response to other inputs over the course of H-reflex conditioning and by analysis of single motoneuron behavior in acute studies of anesthetized conditioned animals.

The particular supraspinal structures and descending pathways responsible for the functional change are obviously of interest. If, for example, change in presynaptic inhibition of the Ia- $\alpha$ -motoneuron synapse occurs, corticospinal, rubrospinal, reticulospinal, or vestibulospinal pathways could be responsible (2, 9, 23). However, until the site and mechanism of the functional change are known, speculation and experimentation concerning the responsible descending pathways are premature.

#### *Location of the memory substrates*

H-reflex change is presumably initiated by change in descending input. In the initial stages of conditioning, change is doubtless simply imposed on a naive spinal reflex arc. However, as discussed above, the animal does not know exactly when the H-reflex will be elicited; and, when it is elicited, it is over well before any other possible CNS response. Thus, for the animal to be successful, the descending activity affecting the spinal reflex arc must be present for many hours each day throughout the many days of HR $\uparrow$  or HR $\downarrow$  mode exposure. A large body of clinical and laboratory data (see INTRODUCTION) suggests that such chronic alteration in descending influence will eventually produce intrinsic persistent spinal alterations, which can remain without further impetus from above. The gradual development and persistence of H-reflex and SSR operant conditioning are consistent with persistent cord change. Both H-reflex and SSR con-

ditioning are even slower than adaptive plasticity in the vestibuloocular reflex (14, 20, 29), which may also involve persistent alteration at or near the level of a reflex arc. As discussed in detail previously (46), the two-phase course of development [also present with vestibuloocular reflex plasticity (25)] is additional support for the occurrence of persistent structural or biochemical change, though not necessarily at the spinal level. If persistent alterations do occur in the cord, they should constitute memory substrates susceptible to physiological, anatomical, and biochemical study at the neuronal and synaptic levels with available techniques. If such alterations occur only at supraspinal sites, such as the cerebellum, they may still be amenable to study. Evidence for persistent spinal alterations is currently being sought in studies of H-reflex amplitude in anesthetized conditioned animals before and after spinal cord transection. The unconditioned leg provides the essential control. Initial experiments in naive animals indicate that these studies should be able to provide the needed data (24, 40).

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