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Memory Traces in Primate Spinal Cord Produced by Operant Conditioning of H-Reflex

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SUMMARY AND CONCLUSIONS

1. Study of memory traces in higher animals requires experimental models possessing well-localized and technically accessible memory traces—plasticity responsible for behavioral change, not dependent on control from elsewhere, and open to detailed investigation. Our purpose has been to develop such a model based on the wholly spinal, largely monosynaptic path of the spinal stretch reflex. Previous studies described operant conditioning of this reflex and of its electrical analog, the H-reflex. In this study, we sought to determine whether conditioning causes changes in the spinal cord that affect the reflex and are not dependent on continued supraspinal influence, and thus qualify as memory traces.

2. Sixteen monkeys underwent chronic conditioning of the triceps surae H-reflex. Eight were rewarded for increasing H-reflex amplitude (HR↑ mode), and eight were rewarded for decreasing it (HR↓ mode). In each animal, the other leg was an internal control. Over several months of conditioning, H-reflex amplitude in the conditioned leg rose in HR↑ animals and fell in HR↓ animals. H-reflex amplitude in the control leg changed little.

3. After HR↑ or HR↓ conditioning, each animal was deeply anesthetized and surgically prepared. The reflex response to supramaximal dorsal root stimulation was measured from the triceps surae nerve as percent of response to supramaximal ventral root stimulation, which was the maximum possible response. Data from both legs were collected before and for up to 3 days after thoracic (T_{9-10}) cord transection. The animal remained deeply anesthetized throughout and was killed by overdose.

4. The reflex asymmetries produced by conditioning were still present several days after transection removed supraspinal influence: reflexes of HR↑ animals were significantly larger in HR↑ legs than in control legs and reflexes of HR↓ animals were significantly smaller in HR↓ legs than in control legs.

5. Reflex amplitude was much greater in the control legs of anesthetized HR↓ animals than in the control legs of anesthetized HR↑ animals.

6. Chronic conditioning had at least two effects on the spinal cord. The first effect, task-appropriate reflex asymmetry, was evident both in the awake behaving animal and in the anesthetized transected animal. The second effect, larger control leg reflexes in HR↓ animals than in HR↑ animals, was evident only in the anesthetized animal. By removing supraspinal control, anesthesia and transection revealed a previously hidden effect of conditioning.

7. The results suggest that conditioning can cause three kinds of CNS plasticity: intended (responsible for increased reward), associated (a by-product of the same processes producing intended plasticity), and compensatory (allowing continued performance of previously learned behavior). The plastic change responsible for task-appropriate reflex asymmetry is intended: it is the change that increases reward probability. The plastic change apparent only in the control leg reflexes of anesthetized animals is probably compensatory.

8. Operant conditioning of the H-reflex produces several plastic changes in the spinal cord that are potentially accessible memory traces. At present, the most probable sites of plasticity are the Ia afferent synapse on the α-motoneuron and the α-motoneuron itself.

INTRODUCTION

Present hypotheses concerning memory begin with the assumption that neuronal activity can produce persistent changes in the central nervous system (CNS). These plastic changes, which could be as striking as the sprouting of new synaptic connections or as subtle as modification in specific membrane ionic conductances, are thought to be responsible for subsequent changes in CNS activity that are expressed as altered behavior (7, 21). This assumption is based in part on the observation that memory can survive prolonged abolition or distortion of CNS activity, as in generalized seizures or traumatic unconsciousness, and thus cannot be attributed simply to continuous activity in a CNS impervious to alteration (16).

Broader support for the assumption that memory results from activity-dependent plasticity comes from growing realization that the events referred to as memory are part of a wide range of activity-dependent CNS plastic changes. Among these phenomena are those occurring during development. The essential role of normal visual input in the proper development of striate cortex is only one particularly prominent example (29). Another class of activity-dependent changes comprises those resulting from injury. For example, the complex sequence of changes in the spinal cord below transection is due in large part to loss of activity in descending pathways (28, 30).

In spite of the close relation between memory and other activity-dependent phenomena, prevailing theoretical and experimental approaches in higher animals focus explicitly or implicitly on the perceived unique features of memory as opposed to other activity-dependent phenomena. Thus attention centers on learning that appears to occur quickly and on CNS structures, like the hippocampus, that seem to play a special role in such learning.

Our approach derives from and relies on the similarity of memory to other activity-dependent CNS plasticity. We assume that, like changes produced by development or trauma, memory traces can occur anywhere in the CNS. In each instance, location depends ultimately on the requirements of the behavioral change, and directly on the pattern of CNS activity occurring during learning. Beginning from

the abundant evidence that the spinal cord is capable of activity-dependent plasticity (see Refs. 28 and 40 for review), we developed an operant conditioning task that demanded chronic change in the tonic descending activity impinging on the spinal cord. The hypothesis was that such chronic change in supraspinal control over the cord would produce activity-dependent plastic changes in the cord itself. Such plasticity, occurring in a relatively well-defined and accessible part of the CNS, could be a particularly felicitous experimental model for the study of memory.

Operant conditioning of H-reflex

The H-reflex, the electrical analog of the spinal stretch reflex, or tendon jerk, is wholly spinal and largely monosynaptic, a product of the two-neuron pathway consisting of the Ia-afferent fiber, the α-motoneuron, and the synapse between them (see Refs. 6 and 26 for review, and see DISCUSSION). H-reflex amplitude, measured by electromyograph (EMG), reflects the number and size of α-motoneurons that fire in response to the afferent input. After initial studies of spinal stretch reflex conditioning (39, 41, 44–46), we trained monkeys on a task that required that they increase (HR↑ mode) or decrease (HR↓ mode) triceps surae H-reflex amplitude without change in background α-motoneuron tone (40). Because the H-reflex was elicited at an unpredictable time, and because it occurred before any other possible CNS response, the task required long-term change in supraspinal control over the spinal arc of the reflex (40). This change in supraspinal influence had to be present for the 5–7 h/day the monkeys spent on the task over study periods of several months. Task-appropriate H-reflex change began in the first day and continued to develop over at least 6 wk. The results suggested that the long-term change in supraspinal influence over the spinal arc of the H-reflex caused gradual plastic changes in the spinal cord. Such spinal cord plastic changes should constitute technically accessible memory traces.

The present study

If operant conditioning of the triceps surae H-reflex does cause plastic changes in the lumbosacral cord, then evidence of such plasticity should remain even after thoracic cord transection removes all supraspinal control. We operantly conditioned the triceps surae H-reflex in one leg over several months, anesthetized and surgically prepared the animal for lumbosacral cord study, measured the reflexes in both legs (conditioned and control), transected the thoracic cord, continued to measure reflexes bilaterally for up to 3 days after transection, and finally killed the still anesthetized animal. To determine whether conditioning had produced plastic changes in the cord, we compared reflexes within animals and across animals. That is, we compared each animal's HR↑ or HR↓ leg to its control leg; and we compared HR↑ and HR↓ animals.

Before beginning this study, we expected to encounter severe reflex depression as part of the spinal shock produced by cord transection. For this and other reasons, we studied the triceps surae H-reflex arc in naive (i.e., unconditioned) anesthetized animals both with and without cord transection over several days (42). We found that cord transection caused little or no reflex depression. Subsequent closer evaluation of the available laboratory and clinical literature showed that this result was not surprising. Most studies have found that the H-reflex, in contrast to the tendon jerk, is minimally depressed by cord transection (see Ref. 42 for review). Thus transection-induced reflex depression was not an obstacle to the present study.

METHODS

Subjects were 16 monkeys (*Macaca nemestrina*, male, 6–9 kg). The chronic techniques used for operant conditioning of the H-reflex are described fully elsewhere (40). They are summarized here. The acute terminal experiments in which conditioned animals were anesthetized and their reflexes studied before and after cord transection are described in detail. All chronic and acute procedures were in accord with Department of Health, Education, and Welfare (DHEW) Publ. No. (NIH) 85-23, "Guide for the Care and Use of Laboratory Animals," and had been reviewed and approved by the Wadsworth Center Animal Welfare Committee.

Chronic operant conditioning of the H-reflex

To prepare each animal for training, chronic stimulating and recording electrodes were implanted under general anesthesia. To elicit the H-reflex from triceps surae, a silicon rubber cuff with embedded fine-wire electrodes (36, 37) was placed around the tibial nerve just above the knee. Fine-wire EMG electrodes were inserted in medial and lateral gastrocnemii and soleus muscles (i.e., triceps surae). In the first seven animals, one leg was implanted and conditioned. In the last nine, both were implanted (though only one was conditioned, see below). The wires from all electrodes passed subcutaneously to a common exit and were attached to a small connector plug. During data collection, each monkey sat on a smooth flexible grid restrained by a loosely fitting Plexiglas collar. Monitored and rewarded by computer, the animal learned to keep triceps surae EMG within a given range. If correct EMG was maintained for a randomly selected 1.2- to 1.8-s period, a 100-μs square-wave voltage pulse, at a strength kept by the computer just above M response (i.e., direct muscle response) threshold, was given to the tibial nerve via the nerve cuff and elicited the H-reflex. The computer digitized EMG for at least 50 ms following the stimulus and calculated the average of the absolute values of the digitized EMG over the H-reflex interval (typically 12–22 ms after stimulus onset). Liquid reward was given 200 ms after the stimulus. Thus the animal held correct triceps surae background EMG for a randomly chosen period, received the nerve cuff stimulus, opened its mouth, and received a reward squirt. The task operated under one of three modes. Under the control mode, reward followed every H-reflex elicitation. Under the HR↑ or HR↓ mode, reward occurred only if the average absolute value of EMG during the H-reflex interval was more (HR↑) or less (HR↓) than a specified value.

Monkeys normally completed 3,000–6,000 trials per day. The computer gave a daily summary, including average background EMG amplitude and average course of EMG amplitude following the stimulus. Daily H-reflex amplitude was defined as average EMG amplitude in the H-reflex interval minus average background EMG amplitude. As noted above, EMG measurement was absolute value (equivalent to full-wave rectification). In addition, raw EMG was recorded on analog tape periodically.

Data were obtained from each animal over 3–6 months. Throughout this period, background EMG and M response amplitude remained stable. For the first 10–25 days, the animal worked under the control mode. It was then switched to the HR↑

mode (eight animals) or the HR↓ mode (eight animals) for 40–161 days.[1]

The nine animals implanted in both legs maintained triceps surae background EMG in both legs simultaneously. Then H-reflexes were elicited from both legs, and EMG data were collected from both legs. However, under the HR↑ or HR↓ mode, reward depended on the H-reflex in only one leg (the conditioned leg). The H-reflex was simply measured in the other leg (the control leg). This measurement assessed the effects of conditioning one leg's H-reflex on the H-reflex of the other leg (43).

Animal well-being was meticulously monitored throughout the study. Food and water consumption, weight, skin condition, and demeanor were closely followed. Complete details of animal care procedures have been published (40, 41). All animals were healthy and active throughout the study period.

Acute study of conditioned animals

After chronic exposure to the HR↑ or HR↓ mode, each animal was prepared for acute terminal investigation. Anesthesia was induced with intramuscular (im) ketamine and atropine and then deepened and maintained with intravenous (iv) pentobarbital sodium. The intravenous line was also used to give required fluid as Ringer lactate [70 ml · kg^{-1} · day^{-1} (15) plus an allotment for the trauma of the surgical preparation]. The animal was intubated and placed in a Kopf stereotactic headholder and spinal frame. Vital signs (including expired CO_2) were monitored and temperature was maintained by a heating pad and a heat lamp. Deep surgical anesthesia (17, 35) was maintained throughout the study. At least one person remained with the animal constantly.

Figure 1 shows the surgical preparation. A L_5-S_1 laminectomy exposed the cauda equina. The triceps surae is supplied principally by roots L_6, L_7, and S_1 (Ref. 18 and our preliminary studies). On each side, the L_6, L_7, and S_1 dorsal roots were tied together 0.5 cm proximal to the L_6 dorsal root ganglion and cut just distal to the tie. The proximal dorsal root bundle on each side was then placed in a silicon rubber cuff with embedded fine-wire stimulating electrodes similar to the chronic cuff implanted around the tibial nerve for operant conditioning of the H-reflex (see above). The intact L_6, L_7, and S_1 ventral roots of both sides were placed in a single cuff with embedded stimulating electrodes. The exposed roots and cuffs were kept covered with warm mineral oil. In each leg, the branches of the tibial nerve supplying the medial and lateral gastrocnemii and the soleus were cut just proximal to entry into the muscle. The ends were tied together, and the distal 0.5 cm of the bundle was crushed with a forceps to allow monopolar killed-end recording. The bundle was placed in a recording cuff comparable to the stimulating cuffs and kept warm and hydrated between recordings by closing the wound over it. (In earlier animals, the entire tibial nerve at the knee was placed in the cuff. In all cases, this recording cuff was distal to the chronically implanted stimulating cuff used to elicit the H-reflex during chronic conditioning.)

After this surgical preparation, we recorded each leg's triceps surae nerve responses to root stimulation according to the following protocol, which was applied first to the right leg and then to the left leg. (Periodically the left leg was studied first, to document that order did not affect results.) The stimulus was a 100-μs supramaximal (5–6 times threshold) voltage pulse delivered at 0.5 Hz. Responses to ventral root (VR) stimulation were recorded first, and several minutes later reflex responses to dorsal root (DR) stimulation were recorded. Then this reflex response to 0.5-Hz DR stimulation was potentiated (by 500-Hz DR stimulation for 20 s) and recorded repeatedly over the next 5 min. Triceps surae nerve recordings were amplified (band pass 1–3,000 Hz), photographed from the oscilloscope screen, digitized (10,000 Hz), and averaged by computer (5 responses excluding the first, which, with DR stimulation, was larger than subsequent responses).

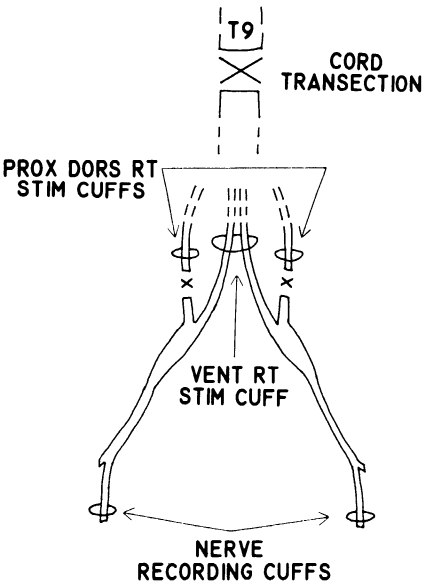

FIG. 1. Surgical preparation. See text for full explanation.

Responses to VR stimulation and to pre- and postpotentiation DR stimulation were recorded hourly from each leg for 3–4 h. Then an additional laminectomy was performed at T_9 and the dura was exposed. The $T_{9\text{-}10}$ cord was cooled with ice water for 8–10 min [to reduce transection-induced excitation (4)], and then completely transected with a scalpel. The cut ends retracted, leaving a 1-cm space that was packed with Gelfoam (Upjohn). Responses to VR and DR stimulation were recorded from each animal every hour for the next 4 h and then at 2- to 5-h intervals for up to 73 h after transection. Fourteen of the 16 animals were followed for over 25 h after transection and 10 for over 45 h. At the completion of recording, the deeply anesthetized animal was killed with an overdose of intravenous pentobarbital sodium and perfused for anatomic study.

RESULTS

In the anesthetized, surgically prepared animal, the response to VR stimulation began 3.5–5.5 ms after stimulation and lasted 1.3–2.3 ms. The reflex response to DR stimulation began at 5.5–8.0 ms and lasted 1.6–2.8 ms. Later, presumably polysynaptic activity was minimal or absent, probably due to the pentobarbital sodium anesthesia. Responses became maximum by three to four times threshold, and measurements were made with stimulus intensity at five to six times threshold. Response amplitudes were measured as area (μV · ms). The reflex response to DR stimulation was divided by the response to VR stimulation (13). Thus reflexes are in percent of maximum possible response (i.e., response to stimulation of every motoneuron axon in the L_6-S_1 ventral roots that passed through the

[1] The first HR↑ animal and the first HR↓ animal were each exposed to the opposite mode (HR↓ or HR↑) for an interval in the midst of HR↑ or HR↓ conditioning, as part of an effort to evaluate reversal of conditioned change. In each case, this reversal interval was a minor part of the total conditioning period, ended more than a month before terminal study, and had no lasting effect on reflex amplitude. Four other animals were reexposed to the control mode for brief intervals in the midst of HR↑ or HR↓ conditioning, again without significant effect on final reflex amplitude.

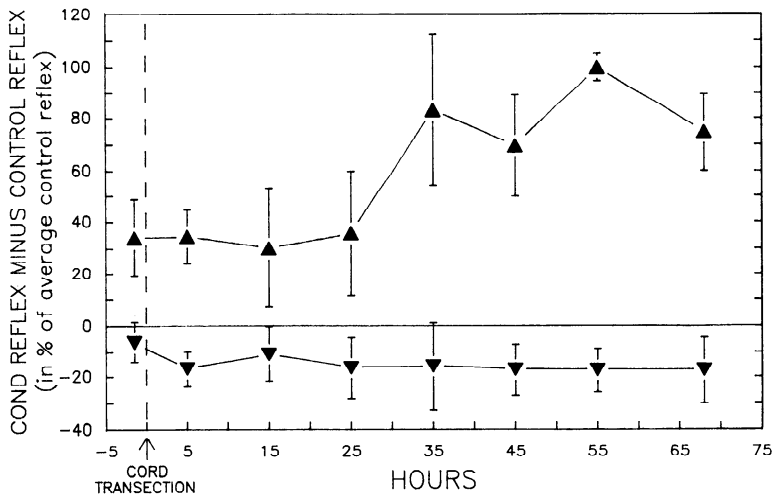

FIG. 2. Average (±SE) differences between reflexes of conditioned and control legs for HR↑ animals (▲) and for HR↓ animals (▼) over the course of study. Differences are expressed in percent of the average amplitude of control leg reflexes from 10 h posttransection on [i.e., when reflexes have stabilized after the initial nonspecific rise (42)]. In HR↑ animals, reflexes are bigger in HR↑ legs than in control legs. In HR↓ animals, reflexes are smaller in HR↓ legs than in control legs. These task-appropriate reflex asymmetries are particularly prominent 2–3 days after transection.

nerve recording cuff). This method of measurement allowed comparison of results across animals, and controlled for any changes in the recording cuffs or in motoneuron axonal function over the study period. Responses to VR stimulation usually fell gradually, declining to ~50% of initial value by 25–30 h and to ~40% by 60 h. Latency and form remained stable. We attribute this amplitude decline to unavoidable deterioration of the cut and distally crushed peripheral nerves. The decline did not appear to affect measurement of reflex response to DR stimulation as percent of response to VR stimulation.

After tetanic potentiation, the reflex response to DR stimulation grew rapidly for ~20 s and then declined back to its original size over 5 min. Potentiation did not remove the inter- and intra-animal reflex differences evident without potentiation (11). Thus, for clarity and simplicity, this presentation focuses on the basic, unpotentiated reflexes.

As previously reported in our study of naive (i.e., unconditioned) animals (42), reflex responses to DR stimulation rose gradually over the first 12–15 h of recording (i.e., until ~10 h after transection) and then remained quite stable. The possible causes of this rise, such as gradual abatement of the effects of the extensive surgical preparation, are discussed in the earlier report (42). In the present study, this rise occurred in both conditioned and control legs, and thus did not prevent assessment of the lasting effects of conditioning. The data also suggested that anesthesia and transection had transient differential effects on conditioned and control reflexes. These effects abated within the first day after transection. This report concerns the persistent effects of conditioning, i.e., those that persisted through the 2–3 days of posttransection study.

HR↑ animals

In HR↑ animals, reflex asymmetry consistent with the effects of the chronic HR↑ conditioning was evident after cord transection. Reflexes were significantly larger in HR↑ legs than in control legs (t = 8.9, df = 136, $P \ll 0.001$). Figure 2 shows average differences (*upward-pointing triangles*) (±SE) between reflexes in HR↑ and control legs of all 8 HR↑ animals over the course of study, expressed in percent of the animal's average control leg reflex from 10 h posttransection on [i.e., when reflexes had stabilized after the initial nonspecific rise (42)]. Task-appropriate reflex asymmetry is particularly prominent several days after transection removes supraspinal control. From 10 h posttransection on, reflexes were 51% larger in HR↑ legs than in control legs. This difference is comparable to the effect of HR↑ conditioning in the awake behaving animal. In the weeks immediately before terminal study, H-reflexes in HR↑ legs averaged 58% larger than their control mode values.

Figure 3 shows reflexes from the HR↑ and control legs of one animal before and 2 days after cord transection. In the

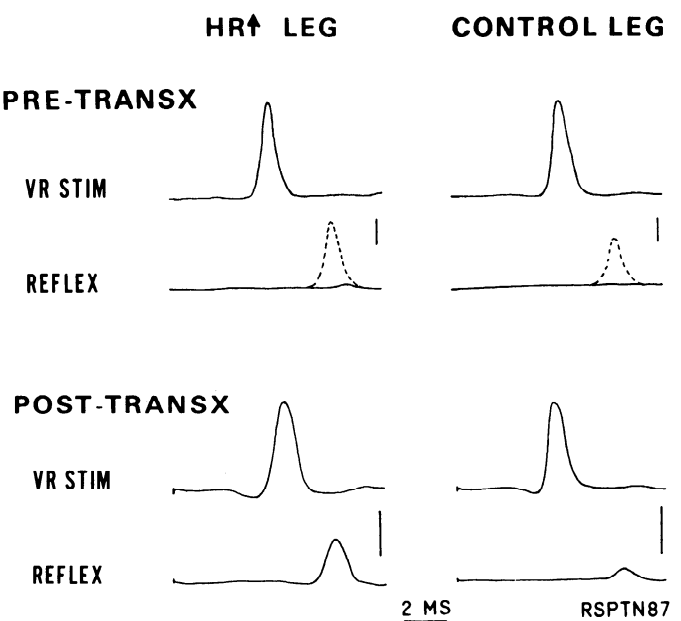

FIG. 3. Responses to ventral root (VR) stimulation and reflex responses to dorsal root (DR) stimulation from an HR↑ animal before cord transection and 2 days after transection. To facilitate comparison of the reflexes, responses are scaled so that responses to VR stimulation (i.e., maximum possible responses) are equal in height. *Vertical bars* are 100 μV. Because the reflex is small (HR↑ leg) or absent (control leg) before transection, pretransection reflexes are also shown 20 s after tetanic potentiation (*dashed*). Reflexes are larger in the HR↑ leg than in the control leg both before and after transection.

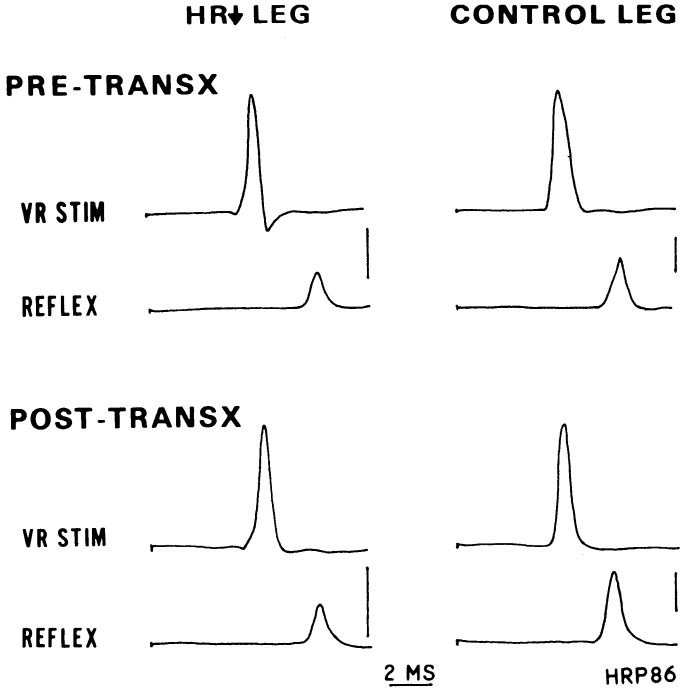

FIG. 4. Responses to VR stimulation and reflex responses to DR stimulation from an HR↓ animal before cord transection and 3 days after transection. To facilitate comparison of the reflexes, responses are scaled so that responses to VR stimulation (i.e., maximum possible responses) are equal in height. *Vertical bars* are 200 μV. Reflexes are smaller in the HR↓ leg than in the control leg both before and after transection.

first recording, before transection, there is no detectable reflex in the control leg and a small reflex in the HR↑ leg. Tetanic potentiation produces sizable reflexes on both sides, and the conditioned asymmetry is still present. After transection and following the nonspecific rise (42), reflexes are substantial on both sides; nevertheless, the HR↑ leg's reflex remains larger.

HR↓ animals

In HR↓ animals, reflex asymmetry consistent with the effects of the chronic HR↓ conditioning was also evident after cord transection, though it was less pronounced than the asymmetry in HR↑ animals. Reflexes were significantly smaller in HR↓ legs than in control legs ($t = 5.6$, df = 189, $P \ll 0.001$). Figure 2 shows average differences (*downward-pointing triangles*) (±SE) between HR↓ legs and control legs from all eight HR↓ animals over the course of study. Task-appropriate reflex asymmetry is still apparent several days after transection removes supraspinal control. From 10 h posttransection on, reflexes in HR↓ legs averaged 19% smaller than reflexes in control legs. This difference is about two-thirds as great as the effect of conditioning seen in the awake behaving animal. In the weeks immediately prior to terminal study, H-reflexes in HR↓ legs averaged 27% smaller than their control mode values.

Figure 4 displays reflexes from the HR↓ and control legs of an HR↓ animal before and 3 days after transection. In the first recording, before transection, the reflex is smaller in the HR↓ leg than in the control leg. After transection, and after the nonspecific rise, reflexes are larger in both legs, and the conditioned asymmetry is more prominent.

Comparison of HR↑ and HR↓ animals

As the previous sections indicate, H-reflex conditioning modified the spinal cord so that conditioned reflex asymmetries were evident even after transection removed supraspinal influence. Comparison of HR↑ animals and HR↓ animals revealed another effect of conditioning. When animals were anesthetized and surgically prepared, control leg reflexes were larger in HR↓ animals than in HR↑ animals. Figure 5 shows average control leg reflex amplitudes of HR↑ animals and HR↓ animals over the course of study, and also shows average reflex amplitude in 11 naive animals (from Ref. 42). The nonspecific rise in the first 12–15 h of study, originally seen in naive animals (42), is evident for both HR↑ and HR↓ animals and does not obscure the difference between them. Before transection, control leg reflexes in HR↑ animals are smaller than reflexes in naive animals ($t = 3.6$, df = 77.5, $P < 0.001$), whereas control leg reflexes in HR↓ animals are much larger than reflexes in naive animals ($t = 3.4$, df = 33.1, $P = 0.001$). After transection, the difference between HR↓ animals and naive

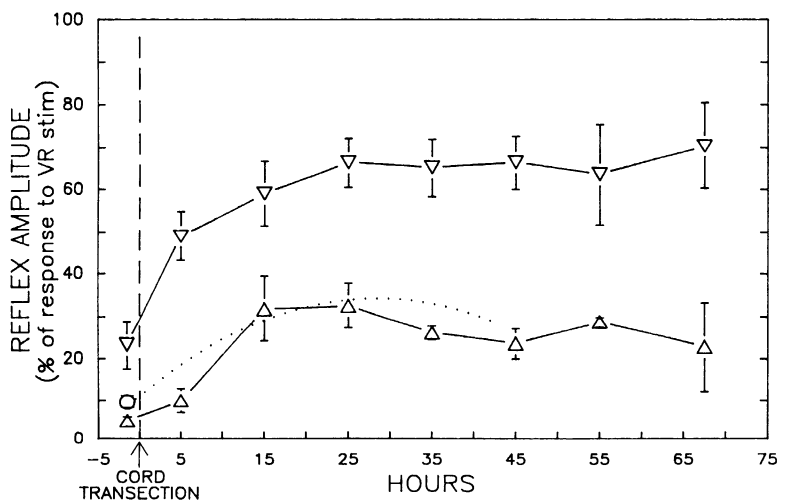

FIG. 5. Average reflexes (±SE) over the course of study in control legs of HR↑ animals (△) and HR↓ animals (▽). Average reflex amplitude (±SE) in naive (i.e., unconditioned) animals before transection is also shown (○), and its course after transection is indicated by the *dashed line* (a computer-fit to the data of Ref. 42). The nonspecific rise in the first 12–15 h of study (42) is apparent in all 3 groups. Throughout the study, reflexes are much larger in control legs of HR↓ animals than in control legs of HR↑ animals.

animals persists, whereas that between HR↑ and naive animals is minimal or absent. The profound difference between control leg reflexes of HR↑ and HR↓ animals obviously persists through the 3 days of study.

In the awake behaving animal, the only major effect of the several months of H-reflex conditioning was appropriate change in the H-reflex of the conditioned leg (43). The H-reflex in the control leg had changed little from its control mode amplitude, so that immediately before anesthesia and terminal study, reflexes were of comparable size in the control legs of HR↑ and HR↓ animals. However, anesthesia and surgical preparation affected HR↑ and HR↓ animals differently, so that control leg reflexes were much bigger in HR↓ animals than in HR↑ animals. It appears that the removal of supraspinal control, first by anesthesia and finally by transection, revealed a conditioned change in the cord that was not apparent in the awake behaving animal.

DISCUSSION

The results indicate that operant conditioning of the H-reflex causes spinal reflex changes that persist for at least 3 days after cord transection removes supraspinal influence. The reflexes were elicited by proximal dorsal root stimulation and measured at the peripheral nerve, so that only the cord and the axons entering and leaving it were involved. Cord transection at T_{9-10} was unequivocally complete: dura and cord were cut and the cut ends of the cord were 1 cm apart. The sole remaining neural connection with supraspinal structures, the paraspinal chain of sympathetic ganglia, is not known to convey supraspinal control to spinal neurons (5). Furthermore, section of the L_6-S_1 dorsal roots removed much sympathetic access to the spinal reflex arc. Extraneuronal, humoral control from supraspinal areas is not a credible explanation because it is not apparent how such blood-borne control could be asymmetric. In addition, related studies indicate that conditioned reflex change is focused in the agonist muscle: synergists are less affected (46). We conclude that the data constitute very strong evidence that H-reflex conditioning produces lasting plastic changes in the spinal cord.

The data also suggest that the cord changes were a major part of the CNS plasticity produced by conditioning. For HR↑ animals, task-appropriate reflex asymmetry in the isolated spinal cord was comparable in magnitude to the effect of HR↑ conditioning in the intact animal immediately before terminal study; and for HR↓ animals, the asymmetry in the isolated cord was about two-thirds as great. In making these comparisons, we must recognize the methodologic differences. In the intact animal, the reflex arc was assessed by the H-reflex, which includes the neuromuscular junction and the muscle itself, is elicited by a submaximal stimulus, and normally requires background EMG activity. In the isolated spinal cord, the reflex arc was assessed more directly. Nerve recording eliminated the neuromuscular junction and the muscle, proximal dorsal root stimulation allowed supramaximal afferent stimulation, and ventral root stimulation provided a maximum possible response against which to measure the reflex response.[2] Because, in both the intact animal and the isolated cord, the effects of conditioning were measured in percent of control values, differences in the absolute amplitude ranges of H-reflexes and nerve responses should not prevent quantitative comparison. The danger in such comparison arises if both kinds of data were gathered over limited response amplitude ranges that differed in their ability to reflect the effects of conditioning. However, in the intact animal, conditioned H-reflex change is not closely correlated with control H-reflex amplitude; and, in the isolated cord, asymmetries were clear whether reflexes were small (in the first 10 h after transection), of moderate size (from 10 h on), or large [after potentiation (Fig. 3 and Ref. 11)]. Therefore, because the data are not limited to specific response amplitude ranges, cautious quantitative comparison is justified. In sum, the data do suggest that task-appropriate asymmetry was as great or nearly as great after anesthesia and transection as before, and thus that the isolated cord contained a substantial memory trace.

Chronic conditioning changes the spinal cord in several ways. First, task-appropriate reflex asymmetry is apparent both in the awake behaving animal and in the anesthetized transected animal. Second, under anesthesia, control leg reflexes are much larger in HR↓ animals than in HR↑ animals. This second effect of conditioning is not evident in awake behaving animals; it is revealed when anesthesia removes supraspinal control. In exploring these changes, the first goal must be to determine where function changes in the reflex arc. The H-reflex pathway is simple and well defined: the number of sites in which function might change is limited.

Possible sites of change

The latency, duration, and predominantly monophasic form of the reflex response to DR stimulation and the characteristic effect of tetanic potentiation indicate that the reflex is produced largely by the monosynaptic pathway consisting of the Ia afferent fiber and the α-motoneuron (22, 25, 26). The possible sites of change in this two-neuron reflex arc are the Ia synapse on the α-motoneuron and the α-motoneuron itself. Whereas these are the most probable sites of plasticity, it should be noted that other pathways may possibly contribute to the reflex (8) and thus could conceivably play a role. However, previous studies (40) and the absence of asymmetry in reflex latency and duration in the present study (see Figs. 3 and 4) suggest that polysynaptic afferent paths have little or no role. The present discussion focuses on the Ia synapse and the α-motoneuron, on how conditioning might produce changes at these sites, and on how such changes might account for one or both of the phenomena observed in the isolated spinal cords of anesthetized transected animals.

The possible mechanisms of reflex change described below are only hypotheses, useful in making the data more

[2] Measurement of H-reflexes in the transected animal would not have made comparison with the intact animal more straightforward, due to unavoidable differences in background tone and/or to the manipulations necessary to provide tone.

explicable to us and to the reader. Alternative mechanisms are conceivable and at this stage may be equally likely.

The conditioned reflex asymmetries

Change in Ia presynaptic inhibition can certainly affect H-reflex amplitude. It is thought to be the mechanism responsible for vibratory inhibition of the H-reflex (1) and may contribute to short-term changes in the H-reflex during performance (12). Decreased and increased presynaptic inhibition could account for the H-reflex change under the HR↑ and HR↓ modes, respectively. Corticospinal, reticulospinal, and vestibulospinal pathways exert supraspinal control over presynaptic inhibition (2, 10, 23). Because the conditioning task elicits the H-reflex at unpredictable times, and because the H-reflex occurs well before any other possible CNS response to the stimulus, a tonic change in such supraspinal control would be necessary. The animal would have to alter descending activity continually over the 5–7 h per day spent on the task. Such constant change in the presynaptic input to the Ia synapse, continuing over weeks and months, might be expected to produce gradual plastic change in the synapse itself (44), change that would persist even after supraspinal control was removed, as in the present study. Such plasticity might include change in bouton size or number, in branch point function (24), or in membrane properties such as those controlling depolarization-induced Ca^{2+} entry and transmitter release. At present, some form of Ia synaptic plasticity, created by long-continued change in presynaptic inhibition, seems a strong candidate for the mechanism of the persistent conditioned H-reflex asymmetries reported here.

Task-appropriate modification of α-motoneuron response to Ia afferent input could be caused by local or general change in the motoneuron. Whereas local postsynaptic changes in dendritic geometry or membrane properties could be responsible (20, 32), we focus here on generalized changes in the motoneuron, such as change in membrane potential and/or membrane resistance.

Membrane potential and resistance are controlled by tonic excitatory and inhibitory inputs reaching the motoneuron from supraspinal and spinal sites. Both affect reflex amplitude: membrane potential by affecting the excitatory postsynaptic potential (EPSP) amplitude required to fire the neuron, and membrane resistance by affecting EPSP amplitude. Membrane potential of the motoneuron population is reflected in the level of background EMG activity, which does not change under the HR↑ or HR↓ mode. However, change in the composition of the tonic inputs responsible for maintenance of this constant background EMG might alter membrane resistance and thereby change Ia EPSP amplitude (12). Alternatively, change in motoneuron recruitment order could modify the population responsible for the background EMG and thus most susceptible to excitation by afferent input (9, 19). This new population could be more (HR↑) or less (HR↓) liable to excitation by Ia input.

The chronic changes in motoneuron inputs underlying these possible mechanisms might eventually produce pre- or postsynaptic plasticity that survives removal of supraspinal control. For example, the membrane potential at which a motoneuron fires or the membrane currents activated by excitatory input might be modified. In sum, a general change in the α-motoneuron could be responsible for conditioned H-reflex asymmetry, but this seems at present a more complicated explanation than change in Ia presynaptic inhibition, because it would have widespread effects on other aspects of motoneuron behavior.

The conditioned change seen only in the anesthetized animal

In the awake behaving animal before terminal study, the only prominent conditioned change is the one required by the task: in an HR↑ animal the H-reflex has increased in the HR↑ leg, whereas in an HR↓ animal it has decreased in the HR↓ leg. Control leg reflexes are little affected by conditioning and thus are similar in awake behaving HR↑ and HR↓ animals in the days before terminal study (43). However, when the animal is anesthetized and transected, the conditioned asymmetry is not the only effect seen. A second effect of conditioning appears: control leg reflexes are much larger in HR↓ animals than in HR↑ animals. Whereas Ia synaptic alteration seems the most probable origin of the task-appropriate reflex asymmetries, a general change in motoneuron function may provide a better explanation for this second change.

Anesthesia and transection affect motoneuron membrane potential, largely because they remove synaptic inputs, particularly those from supraspinal areas (3, 14, 33, 38). Motoneuron membrane potential, and thus susceptibility to Ia excitation, is left dependent on the motoneuron itself and on remaining segmental inputs. If these elements are altered during H-reflex conditioning, effects like those seen in Fig. 5 might be expected. That is, motoneuron membrane potential, and thus motoneuron response to Ia input, could be different in HR↑ and HR↓ animals. But, if we assume that Ia synaptic plasticity is responsible for the task-appropriate reflex asymmetries, why would change occur in these other elements? Furthermore, whatever the mechanisms of the reflex asymmetries, why would HR↑ or HR↓ conditioning produce plastic change apparently unrelated to task-appropriate H-reflex change in the conditioned leg? Consideration of the other demands made by the task and of the demands of other tasks provides a possible answer.

This presentation has emphasized the demand imposed by the HR↑ or HR↓ mode: that H-reflex amplitude change appropriately. But the task, under control mode as well as under HR↑ and HR↓ modes, makes another demand: it requires that background EMG, and thus ongoing α-motoneuron activity, remain at a specified level. Maintenance of this required EMG over the months of control mode and HR↑ or HR↓ mode exposure might produce changes in the cord that would be reflected in a difference between the legs of naive animals and the control legs of conditioned animals. However, this hypothesis cannot account for the difference between control legs of HR↑ and HR↓ animals. This difference may arise from interaction between the two demands (H-reflex change and no change in background EMG) made by the HR↑ and HR↓ modes.

Under the control mode, the animal presumably achieves required background EMG through an appropriate combination of tonic supraspinal and spinal excitatory and inhibitory synaptic inputs to triceps surae motoneurons. Imposition of the HR↑ or HR↓ mode, with the new demand to alter H-reflex amplitude, almost certainly disturbs this combination of tonic motoneuron inputs. For example, change in Ia synaptic function, in response to the HR↑ or HR↓ mode, would affect background Ia synaptic input coming from ongoing muscle spindle activity (27, 31). In addition, if change in Ia presynaptic inhibition is the mechanism for task-appropriate H-reflex change, associated change (34) in postsynaptic inhibition would further disturb the combination of tonic motoneuron inputs responsible for background EMG. Thus the HR↑ and HR↓ modes probably demand more than change in the H-reflex. They also compel the CNS to adjust its control of background EMG.

This adjustment would have to be present 5–7 h/day over the several months of HR↑ or HR↓ mode exposure. Thus it might produce plastic change in spinal interneurons supplying synaptic inputs to motoneurons, in synaptic contacts on motoneurons, or in triceps surae motoneurons themselves. These changes would be different under HR↑ and HR↓ modes and, therefore, could account for the difference exposed by anesthesia and transection. This plasticity might best be labeled compensatory: it allows continued satisfaction of an old task demand, background EMG maintenance, in spite of the side effects of change needed to satisfy a new demand, H-reflex modification.

Alternatively, or in addition, the plasticity responsible for the task-appropriate reflex asymmetries might disturb the performance of other tasks involving the triceps surae or closely related muscles. Such disturbances could also provide the impetus for compensatory plastic changes.

If such compensatory plasticity occurs, it is to some extent bilateral because control leg reflexes are clearly affected (i.e., Fig. 5). However, the effect would presumably be greatest on the conditioned side. Thus the reflex asymmetries measured in anesthetized transected animals may underestimate the actual asymmetries at specific locations, like the Ia synapse. In this regard, it is of note that the increase in control leg reflexes of anesthetized HR↓ animals over reflexes of naive animals is much greater than the decrease in control leg reflexes of anesthetized HR↑ animals and persists after transection (Fig. 5); whereas reflex asymmetry is greater in HR↑ animals than in HR↓ animals (Fig. 2).

Conditioned plasticity, behavioral changes, and memory traces

The results indicate that operant conditioning of the H-reflex in one leg causes several plastic changes in the spinal cord and that their expression in behavior is dependent on the circumstances of testing. The conditioned reflex asymmetry is visible both in the awake behaving animal and in the anesthetized transected animal, whereas the difference in control leg reflexes is visible only in the latter.

This study, like many other memory studies, set out to define the CNS plasticity caused by conditioning and responsible for the behavioral change demanded by the conditioning task. The present data indicate that this standard goal grossly oversimplifies the problem. Conditioning can produce more than the plasticity responsible for the task-appropriate change in behavior. It should be considered capable of producing three kinds of plasticity: intended, associated, and compensatory. Intended plasticity is that responsible for the behavioral change conditioned, in this case appropriate H-reflex change in the conditioned leg of the awake behaving monkey. Associated plasticity results from the processes producing the intended plasticity but is not itself responsible for the intended behavioral change. Plasticity responsible for the modest changes in the reflexes of synergist muscles (46) fits this category. Compensatory plasticity is that needed to allow the CNS to perform previously learned behavior in spite of the intended and associated plastic changes. The plastic changes responsible for the difference between control leg reflexes of anesthetized HR↑ and HR↓ animals are probably compensatory; that is, they may allow the awake behaving animal to maintain correct background EMG and/or to continue to perform other tasks, in spite of the side effects of the intended plasticity.

The occurrence of these several plastic changes ensures that the behavioral effects of H-reflex conditioning are not limited to the adaptive change intended, H-reflex increase or decrease in the conditioned leg. Rather, the behavioral change observed is dependent on the circumstances under which it is measured. In the awake behaving animal, a task-appropriate reflex asymmetry is seen. In the anesthetized transected animal the asymmetry remains, and, in addition, control leg reflexes are altered.

Which of these spinal cord plastic changes is the proper object of study? Presumably both of them, because both are CNS effects of the conditioning procedure. Which is a memory trace, i.e., is responsible for behavioral change? One or both, depending on the circumstances of testing. The plastic change responsible for task-appropriate reflex asymmetry is a memory trace in the awake behaving animal and in the anesthetized transected animal. The plastic change responsible for change in control leg reflexes is a memory trace only in the latter. The designation of a conditioned CNS plastic change as a memory trace, as responsible for a certain behavioral change, requires specification of the circumstances in which behavior is tested. Thus a conditioning procedure, such as operant conditioning of the H-reflex, does not produce memory traces per se; it produces plastic changes that, depending on circumstances, may serve as memory traces.

The present findings emphasize the extreme importance of simplicity and accessibility in experimental models used to study memory on neuronal and synaptic levels. Conditioning of the simplest possible CNS behavior, the H-reflex, causes several plastic changes in the spinal cord alone, and their behavioral effects depend on the circumstances of testing. The isolation, accessibility, and relative simplicity of the spinal cord will be crucial to successful exploration of these cord changes and their mechanisms.

Conclusion

Operant conditioning of the H-reflex modifies the spinal cord. It causes changes in spinal reflex pathways that remain after cord transection removes all supraspinal control. These plastic changes in the cord alter behavior as demanded by the conditioning task, and in other ways as well. Because they are produced by conditioning and affect behavior, they are memory traces. Because they are in the cord, they should be accessible to investigation with available physiologic, anatomic, pharmacologic, and biochemical techniques.

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