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SPREAD OF DAMAGE PRODUCED BY ELECTROLYTIC LESIONS IN THE HYPOTHALAMUS[1]

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Two experiments demonstrated progressive and systematic expansion of behavioral deficits caused by electrolytic lesions in the rat hypothalamus. The effects continued to develop over several hours of testing after lesioning. The expansion affected electrical brain stimulation. Thresholds for positive and aversive brain stimulation rose and the intensity–response functions for self-stimulation changed progressively. The effects appear unrelated to general debility since contralateral stimulation was unaffected. A second experiment showed systematically developing deficits in ingestive behavior. Immediate or quickly developing deficits in water drinking were followed by rejection of liquid food and less palatable solid food. Motor coordination progressively deteriorated. The phenomena provide a tool for systematic analysis of deficits and perhaps prediction of the course of recovery.

The behavioral phenomena to be described in this report indicate a progressive development or expansion of brain lesions during a period of several hours following an electrically produced trauma. The effects were first noted by chance in a study of recovery of function in the rat after hypothalamic damage. The particular index of recovery used was the behavioral response to electrical brain stimulation.

The effects of such stimulation were first assayed in intact animals. Lesions were produced at the site of stimulation and the decrements in response were evaluated in the hours immediately following the lesions and on subsequent days. A significant feature of this study was that the lesions were made with chronically implanted electrodes so that the same electrode used for testing brain stimulation effects prior to lesions could be used for administering the lesioning current. This meant that lesions could be made under brief ether anesthesia from which the animals recovered in a matter of minutes. It was therefore possible to record behavioral evidence of brain damage by stimulating through the same electrode within an hour of the production of the lesion without serious concern for artifacts arising from surgery or anesthesia.

It quickly became evident that the decrements in the effectiveness of electrical brain stimulation did not reach their maximum value at once, for the thresholds for responses to electrical brain stimulation were radically higher 24 hr. after the lesion than after 1 or 2 hr.

This report documents such an effect in more detail, using electrical brain stimulation as an index of the expansion of the lesion (Experiment 1). It also shows (Experiment 2) that a similar graded effect following lesions may be observed in feeding and drinking behavior.

Experiment 1

Method

Subjects. The subjects were 3 mature female albino Sprague-Dawley rats from Charles River Breeding Laboratories, (Wilmington, Massachusetts), weighing approximately 300 gm. at the start of the experiment. They were housed individually and maintained on a normal light/dark cycle.

Electrode placement. All rats had been implanted bilaterally with electrodes whose tips were intended to be in the vicinity of the ventromedial nuclei of the hypothalamus. The electrodes were Formvar-coated stainless steel 0-0 insect pins that had been cleared of insulation over .5 mm. of their tips.

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Prelesion status of electrodes. Prior to the creation of lesions the behavioral effect of stimulation in the ventromedial hypothalamus was established by 2 techniques. (*a*) *Conventional self-stimulation:* The animals were trained to press a lever that produced a .5-sec. train of negative-going square-wave pulses of .1 msec. duration at 100 impulses/sec. This is illustrated diagrammatically in the top half of Figure 1. Training was continued until this behavior was stable and thresholds could be established. (*b*) *Reward and escape procedure* (see the bottom half of Figure 1 and also Figure 2): The rats were subjected to continuous stimulation for 20 sec. followed by 20 sec. without stimulation. If the current intensity was quite low, the animal paid no apparent attention to it, responding not at all (top line in the upper half of Figure 1). At higher stimulation intensities, the rat could respond in 2 ways. Responses on one lever turned stimulation on when it was off (rewarded responses, illustrated in line 2 in the lower half of Figure 1); on a second lever 12 in. away in the opposite corner of the experimental chamber, responses during stimulation terminated it (escape responses, illustrated in line 3 in the lower half of Figure 1). At sufficiently high levels of intensity of stimulation, the animal might show both rewarded and escape responses (line 4 in the lower half of Figure 1), turning stimulation on when it was off by pressing one lever, then very quickly turning the stimulation off again by pressing the other lever.

This procedure, based on that of Margules (1966), yields latency measures of both the aversive and positively reinforcing properties of extended brain stimulation. As shown in Figure 2, a well-trained animal (VS1) responded quite predictably at various levels of intensity of ventromedial hypothalamic stimulation. At lower levels (.05 ma. for example), the animal did not respond on either lever, yielding a response latency of 20 sec. on each lever. At a higher intensity (.2 ma. for example), the animal responded quite rapidly (usually 6–7 sec.) to turn stimulation off (escape), but did not turn the stimulation on at all when it was off. This suggests that with a ventromedial placement, a negative reinforcement system in the brain is being stimulated at first (R. S. Wampler and P. Teitelbaum, unpublished observations, April, 1957). At a still higher intensity (.3 ma. in Figure 2), the animal not only turned stimulation off almost immediately (about 2 sec. latency) when it was on, but also very quickly turned it back on (10 sec. latency) when it was off. This suggests that with higher intensities of stimulation, a positive reinforcement system is also being stimulated, perhaps by spread to the lateral hypothalamus (Margules, 1966; Olds & Olds, 1963).

Lesions. When stable thresholds for brain stimulation had been established, the animals were anesthetized with ether and electrolytic lesions were created using a 1 ma. direct anodal current for durations of 3.3–10 sec. All animals regained consciousness within a minute and were returned to their home cages for a short period (30–45 min.) prior to further testing. All lesions were made at approximately 11 a.m. The animals were kept in their home cages with full access to water and food pellets before and after the lesion and for brief periods between test sessions throughout the following afternoon and evening.

Histology. At the end of the experiment, the animals were anesthetized with Nembutal and perfused through the heart, first with physiological saline, then with 10% Formalin. The brains were removed and stored in Formalin. Then they were embedded in Parlodion and 30 μm. thick sections were cut. Every fourth and fifth section was saved and stained alternately with cresyl violet to reveal cell destruction, or with the Mahon stain to reveal damage to myelinated fibers.

Results

In all 3 subjects (VS1, VS2, and VS3) with ventromedial hypothalamic stimulation, there was evidence of stimulation of both positive and negative reinforcement systems. In all 3 animals, as typified by VS1 and VS2 in Figure 3, the prelesion threshold of the aversive effect was lower than that of the reward effect, suggesting that in the region of the ventromedial hypothalamus, a negative reward system is very densely represented (Stein, Wise, & Berger, 1972).

Postlesion effects. As shown in Figure 3, the lesion current (1 ma. for 10 sec.) produced an initial decrement at 1 hr. in the first 2 animals studied (Animals VS1 and VS2). In Animal VS1, whose thresholds for escape and reward were both measurable preoperatively, there was a larger decrement in the aversive threshold than in the positive threshold. In Animal VS2, to which stimulation was more aversive (as judged by a lower threshold for escape), it was apparently so negative at all intensities that no positive reward effect could be demonstrated (the animal would never turn the stimulation on) within the limits of intensity that were feasible.

Determinations at 24 hr. (also in Figure 3) showed that in both these animals the threshold for both positive and aversive behavioral effects were above the upper limit of stimulation that it was feasible to administer. Brain stimulation at these levels (.1 msec. pulses at 100 pps at 1 ma.) commonly produced convulsions or strong motor automatisms. It therefore appeared that the effect of passing destructive current through brain tissue was much more severe

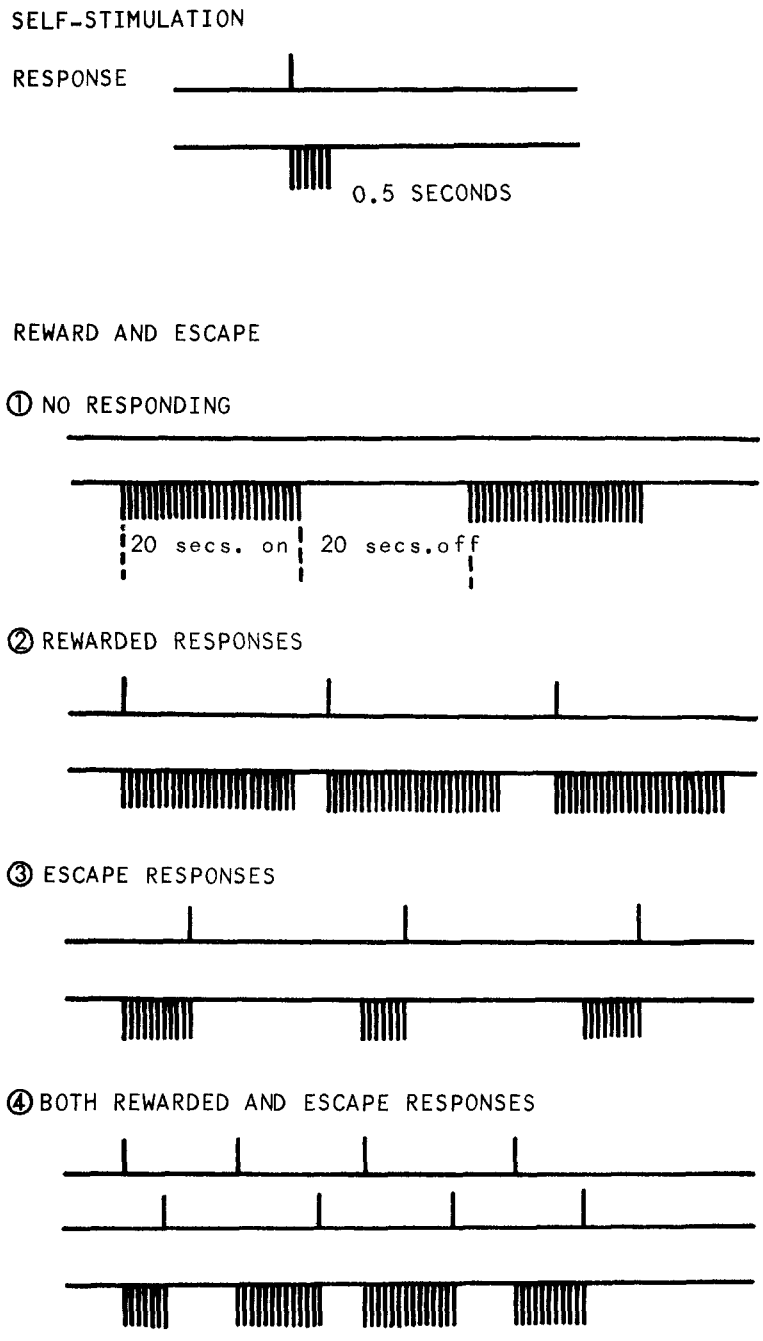

FIG. 1. Procedures for the assessment of positively reinforcing and aversive brain stimulation. (Above, self-stimulation; below, reward and escape procedure. Responses are shown as single vertical lines. The clusters of lines indicate the duration—but not the actual frequency—of brain-stimulation pulses.)

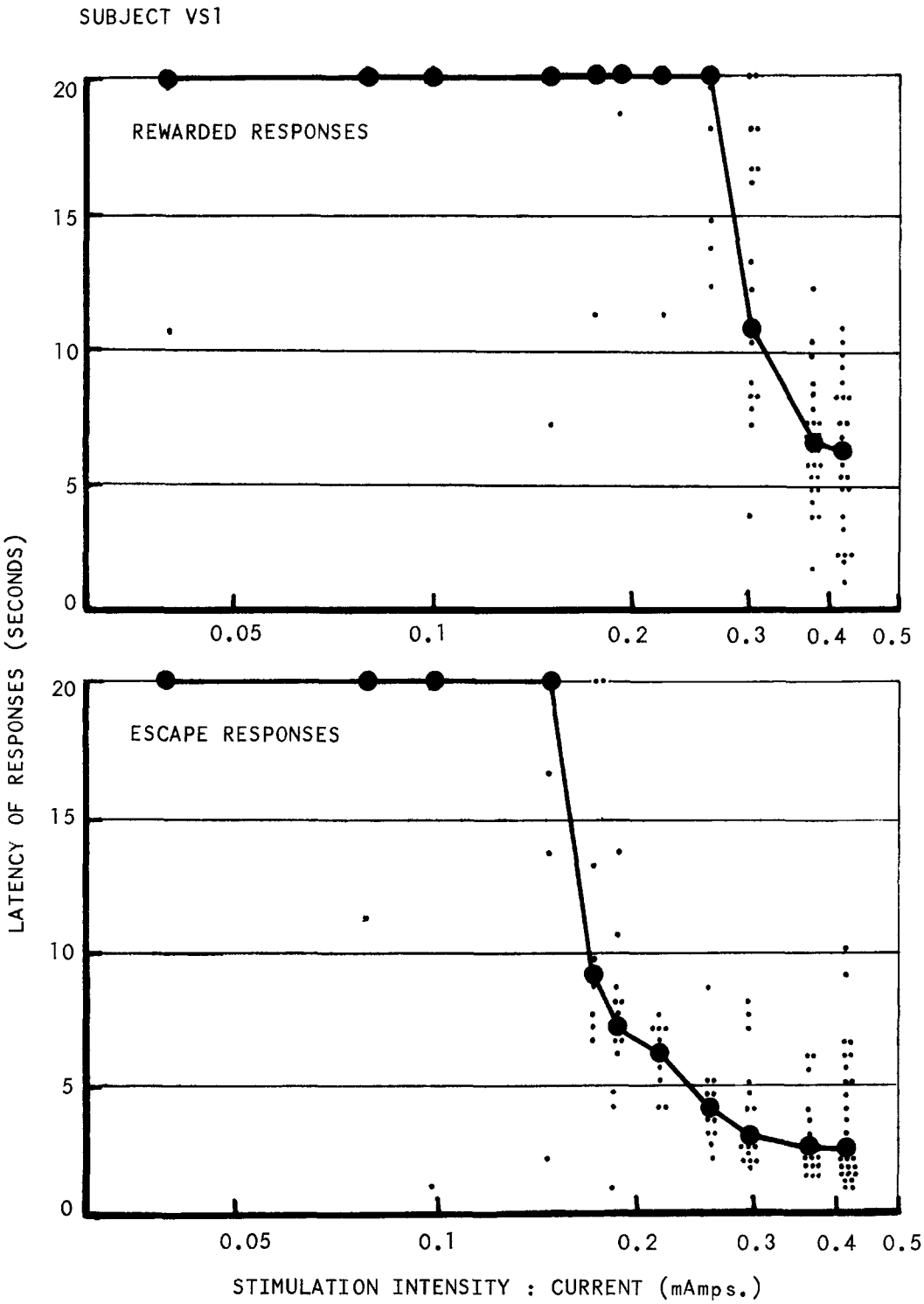

FIG. 2. Stable responding of Subject VS1 showing latency across various intensities of stimulation of positively reinforced responses (top) and of escape responses. (Each point represents a response. The curves join median values at each intensity level tested. These data are from a single testing session.)

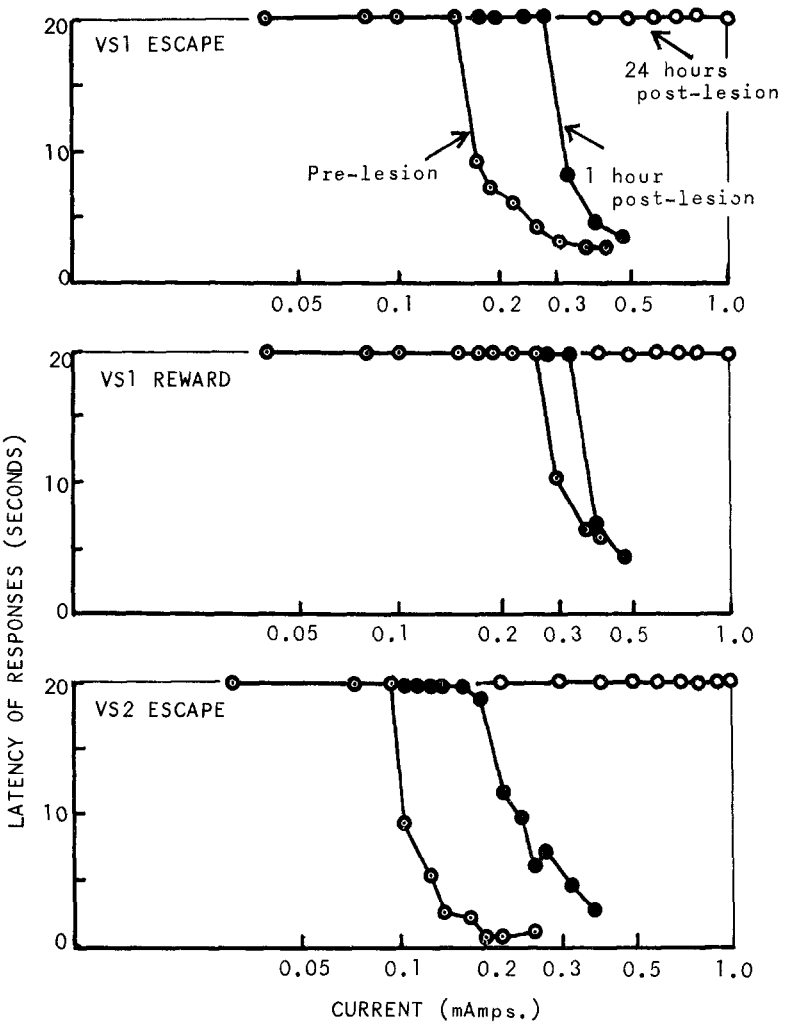

FIG. 3. Thresholds of escape behavior (Subject VS1, top) and of positively reinforced and escape behavior (Subject VS2, middle and bottom). (In each box are shown thresholds before the lesion, 1 hr. after lesion, and 24 hr. after lesion.)

24 hr. later than it had been 1 hr. following the injury.

To study this phenomenon more closely, determinations of positive and aversive effects of stimulation were made with the Margules (1966) procedure in a third animal (VS3) at approximately hourly intervals for 5 hr. following a lesion of 1 ma. for 10 sec. in the left ventromedial hypothalamus, with a final measurement at 24 hr., yielding the family of thresholds shown in Figure 4. Some days later, a second lesion (1 ma. for 3 sec.) was produced in the same animal in the right ventromedial hypothalamus and similar measurements were made. The results were so similar that the effect on the left side can serve as a typical example.

As shown in the left half of Figure 4, before the lesion, stimulation through the ventromedial hypothalamic electrode seemed to be almost purely aversive—the animal turned the stimulation off but rarely turned it on, no matter how high the intensity of stimulation. Following the lesion, the aversive threshold rose hour after hour, so that by 5 hr. and also at 24 hr., little or no aversiveness could be demonstrated through

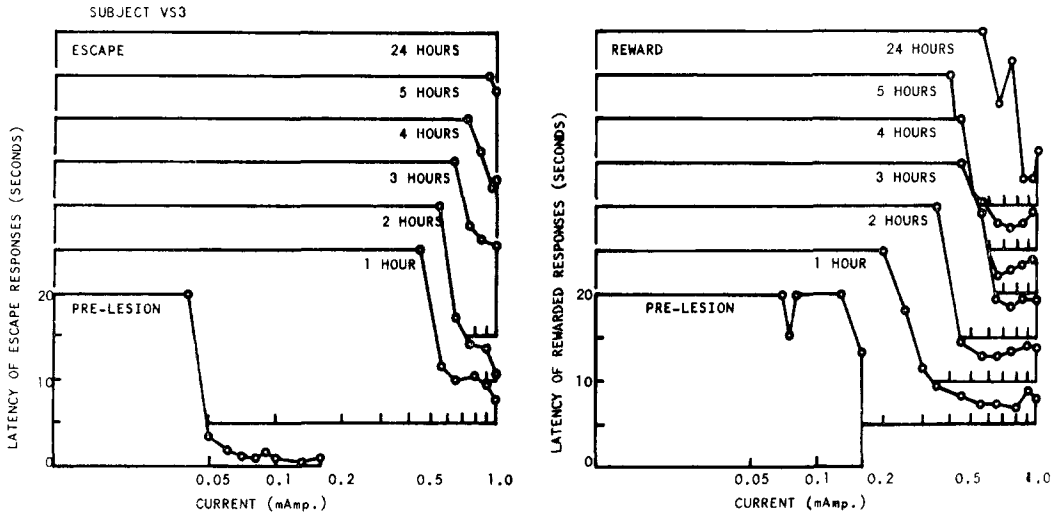

FIG. 4. Positive and aversive effects of stimulation measured before lesioning and hourly after the lesion for Subject VS3. (The uppermost curves show threshold determinations on the following day.)

that electrode. The right half of Figure 4 shows that although little reward effect of stimulation through the ventromedial electrode could be demonstrated in the intact tissue, at 1 hr. following the lesion the animal would turn the stimulation on with short latency at a stimulation intensity well below the now elevated aversive threshold. The threshold for the rewarding effect of stimulation also rose hour after hour, so that by 24 hr., the reward effect was substantially reduced. The time course of the threshold changes was not identical for the functions describing the rewarding and aversive effects. In general, both types of thresholds rose rapidly at first and then less quickly. However, the decrements in aversive functions were on the whole more rapid and extreme. This resulted in a reversal of the relative salience of reward and aversive effects of stimulation, so that electrodes that prior to the lesion had a predominantly or even wholly aversive effect, had after the lesion a lower threshold for rewarding effects than for aversive effects.[3]

Thresholds for self-stimulation (responses rewarded with .5-sec. trains of pulses) also rose progressively following the lesions. At the 2 sites at which the animals displayed consistent self-stimulation the history of change was similar, namely, an initial decrement in sensitivity followed by a further progressive rise in threshold over 5–7 hr. In both cases the upper limit of acceptable current intensity also rose and the rate of response to high intensities increased. This was shown particularly clearly in Subject VS3 (Figure 5). The form of behavior displayed by the subjects at high current levels suggested that the rise in rate was associated with the declining aversive effects of the brain stimulation. (Animals self-stimulating in this experimental situation frequently turned toward the corner of the chamber where they previously responded to turn off brain stimulation, indicating that even the .5-sec. trains of stimulation that they themselves initate may be somewhat aversive.) On the following day the self-stimulation behavior in both these subjects was minimal or nonexistent.

Discussion

These results suggest that damage in the hypothalamus produces an initial loss of function that progressively increases for at least several hours afterwards. We interpret

[3] In one animal an RF lesion was produced at a ventromedial site. The lesioning instrument did not provide a reliable indication of current, but a similar progressive change in thresholds for brain stimulation from 1–24 hr. resulted from the lesion.

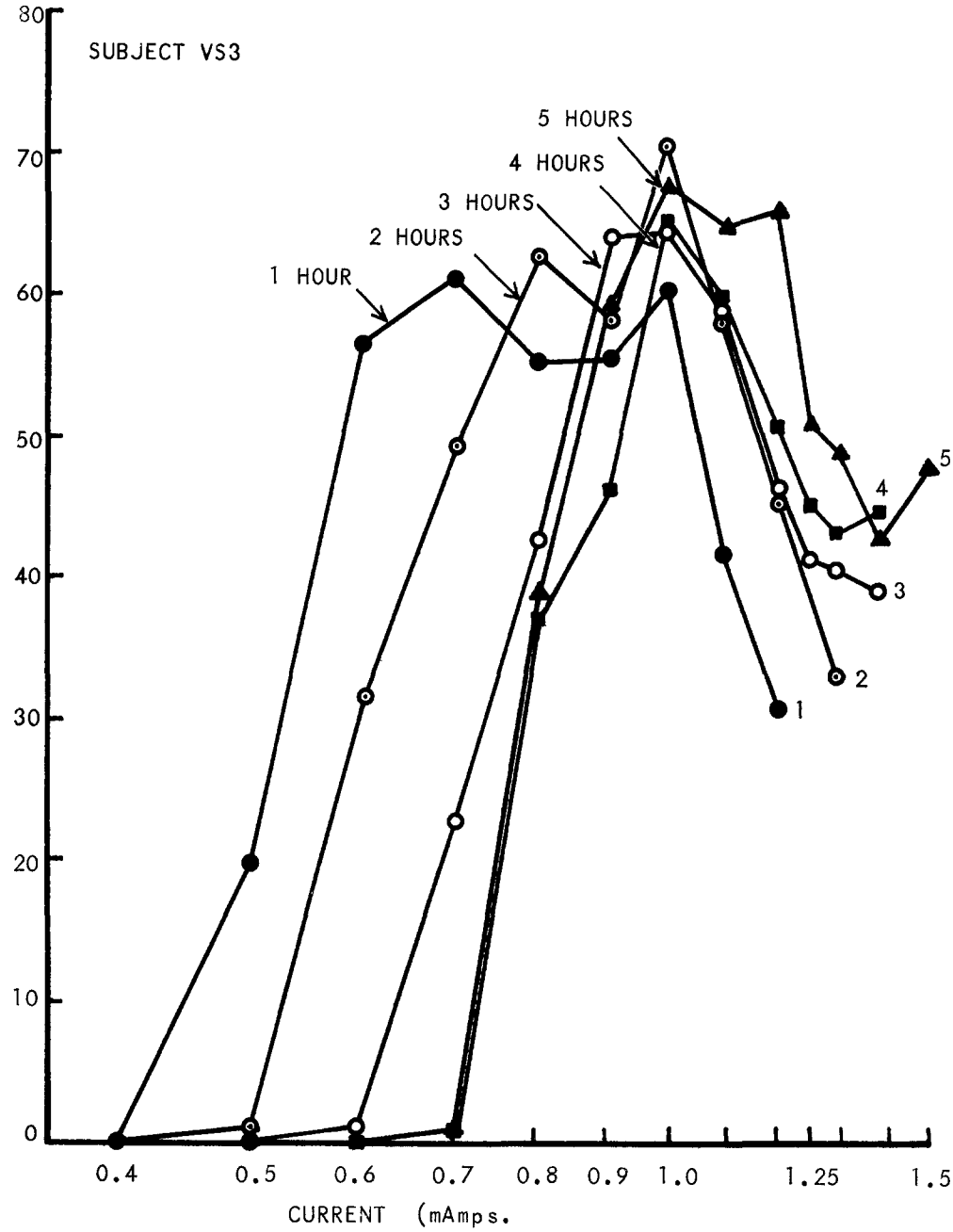

FIG. 5. Rate of response for .5-sec. trains of positive stimulation in Subject VS3 measured at hourly intervals after lesioning.

these effects as reactions to injury in the tissue immediately adjacent to the electrode. However, before speculating further on the nature of these changes, let us consider alternative interpretations.

Whenever we use behavior to assess the effect of brain damage, there is always the possibility that a general behavioral impairment produced by a given lesion yields a deterioration in the particular aspects of be-

havior we are studying. Thus, one might argue that instead of a local decrease in responsiveness of hypothalamic tissue after injury, the elevated behavioral thresholds of bar pressing to turn on or off stimulation merely reflect the animal's generally increasing malaise or debility after brain injury.

In all 3 animals (VS1, VS2, and VS3), thresholds for aversiveness (escape) and for reward (VS1) were measured whenever possible on the *contralateral* side immediately following each determination pre- and postoperatively on the ipsilateral side. As shown in Figure 6, at 24 hr. following damage, when no reward or aversive property of stimulation at the site of injury could any longer be demonstrated, the threshold in the contralateral ventromedial hypothalamus remained quite unchanged. Therefore, the elevation in the threshold on the injured side is due to a local tissue change, not general debilitation or malaise.

Such local changes in brain tissue are quite consistent with the histological observations of Wolf and DiCara (1969), who showed that the size of an electrolytic lesion was much greater at 24 hr. than at 1 hr. following the injury. However, they interpret these changes as due to structural deterioration in the 24 hr. after injury in a ring of cells "fixed" by the current (functionally dead but structurally still intact). Our finding that threshold progressively rises suggests instead that the surrounding tissue is deteriorating functionally as well as structurally. However, one might argue that the interpretation of Wolf and DiCara is correct and that our results are merely an artifact of the use of electrical stimulation. Thus, the axons of the cells "fixed" by the current and functionally dead could be artificially stimulated to activity by electrical stimulation, and with the passage of time greater intensities of current would be required to artificially stimulate progressively deteriorating fibers. To decide this issue in the next experiment we measured the effects of hypothalamic damage in normal feeding and drinking to determine whether the effect increased with time after injury.

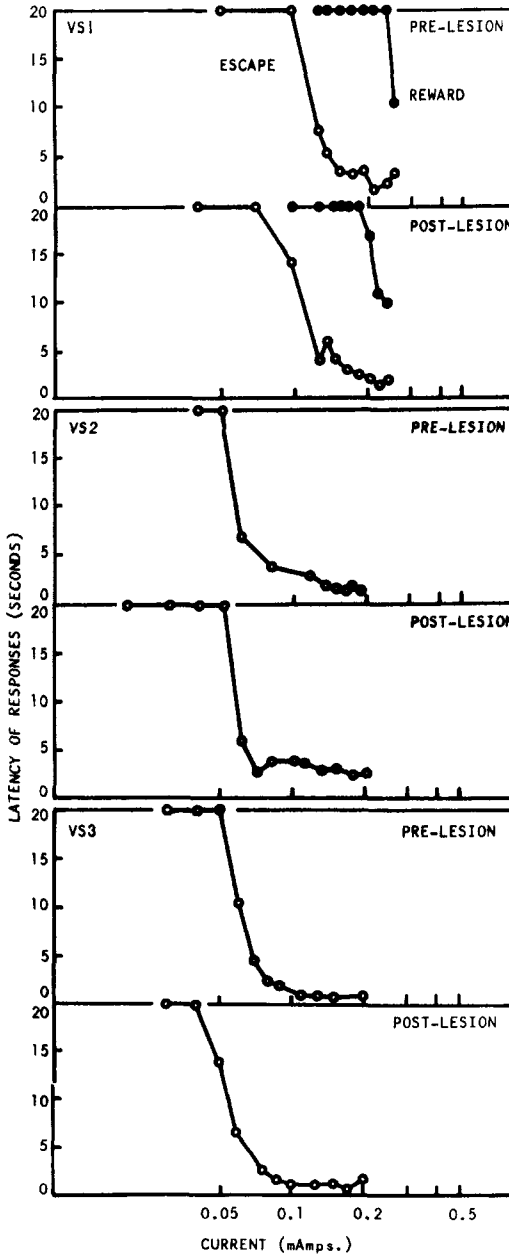

FIG. 6. Effects of lesioning on escape and rewarded response latencies at electrode site contralateral to the lesion.

EXPERIMENT 2

In this study the effects of lesions on feeding and drinking behavior were assessed by exposing deprived animals to water and to a range of food substances during the

hours following lesions in the lateral hypothalamus.

Method

Prelesion regimen. All animals (the same sex, weight, and strain used in Experiment 1) were placed on a regimen in which they were fed food pellets and given water for 1 hr. each day between 1 and 2 p.m. for a minimum of 1 wk. prior to the production of lesions. Four control animals were subjected to the same treatment. During this time all animals were presented on at least 2 occasions with the range of food substances with which they were subsequently tested to accustom them to the foods and testing dishes. All animals ate promptly from these dishes during these exposures.

Lesions. As in Experiment 1, electrolytic lesions were made bilaterally through the previously implanted electrodes under brief ether anesthesia. However, these lesions were placed in the lateral hypothalamus (with skull level, the stereotaxic coordinates were 6.0 mm. anterior, 2.0 mm. lateral to the midline sinus, and 8.0 mm. below the surface of the cortex). Lesion current was held at 1 ma. and duration varied 5–30 sec. The control animals were anesthetized for a similar period of time and showed similar recovery from anesthesia. Lesions were made between 11 a.m. and noon, and testing followed throughout the day.

Testing. The animals were returned to their home cages after hypothalamic damage (or anesthesia). The first testing was begun usually within 30 min. of the lesion. No food or water was available except that offered during testing. A series of food substances were presented to each animal in the following order: (*a*) Purina pellets scattered on the cage floor, (*b*) a liquid eggnog diet (Williams & Teitelbaum, 1959), (*c*) Pablum mixed with Similac and water to a liquid consistency, (*d*) Pablum mixed with Similac to a firm consistency, and (*e*) chocolate chip cookies moistened with water (Teitelbaum & Epstein, 1962). With the exception of the pellets, all food was presented in the same small open glass dishes to which the animals had been habituated prior to lesioning. In addition, water was offered in a Richter tube and in an open dish. In the Richter tube the water level was maintained about 2–3 mm. below the lip of the tube to standardize the difficulty of licking.

The water was offered first and then the food substances in the order described above. If the animals ate or drank, the food or water was withdrawn and the next item introduced almost immediately. If the animals did not approach the food or water, they were either picked up and placed close to the dishes or Richter tube or these were moved closer to the animals. In most instances, water was presented again at the end of the series.

This testing procedure was continued at 30 min. and later hourly intervals throughout the afternoon and evening. Control animals and lesioned animals that continued to eat received only small amounts of test food throughout the day. There was little evidence that the animals' motivation to eat was substantially affected by having food removed while they were eating, and in most cases they were interrupted in their eating by the presentation of a more palatable food. In a few instances, animals that did not accept food from dishes were offered food on a spatula.

Observations were made of licking, spillage, walking in food or water dishes, and the incidence of displacement responses (Tinbergen, 1951) such as rubbing the cage floor and walls with the jaw or paws.

Results

Control Animals. All 4 control animals accepted water and all foods promptly and consistently at every testing session throughout the day after ether anesthesia of equivalent duration to the experimental animals. The only noticeable change that occurred was a progressive tendency to hold the edges of the food dishes as these were withdrawn from the cage.

Experimental animals. The pattern of deficits in drinking and feeding behavior was not completely consistent from animal to animal, yet a general trend is clear. By and large, animals showed rapidly developing, if not immediate, postlesion deficits in drinking. Deficits in feeding behavior followed. These extended over a period of 4–8 hr. and the rapidity of their onset was related to the size (i.e., current duration) of the lesion. The longer the current duration, the more rapid was the development of feeding and drinking deficits. With Subject F8, bilateral lesions at 1 ma. for 30 sec. produced a deficit within 30 min. in drinking from both Richter tube and open dish and in accepting food pellets. After 1 hr. the animal accepted Pablum and moist cookies but not liquid diet. After 2 hr. this subject accepted only moist cookies from a dish, after 4 hr. accepted cookie only on a spatula, and after 5 hr. accepted no food or water and pushed the spatula away when it was placed near its mouth.

Figure 7 reviews the temporal progress of the other experimental subjects and shows that there is a consistent trend in the order of foods that are accepted or rejected. This overall pattern is not entirely consistent, however, and the evidence suggests that the lesions did not produce unitary effects. Defi-

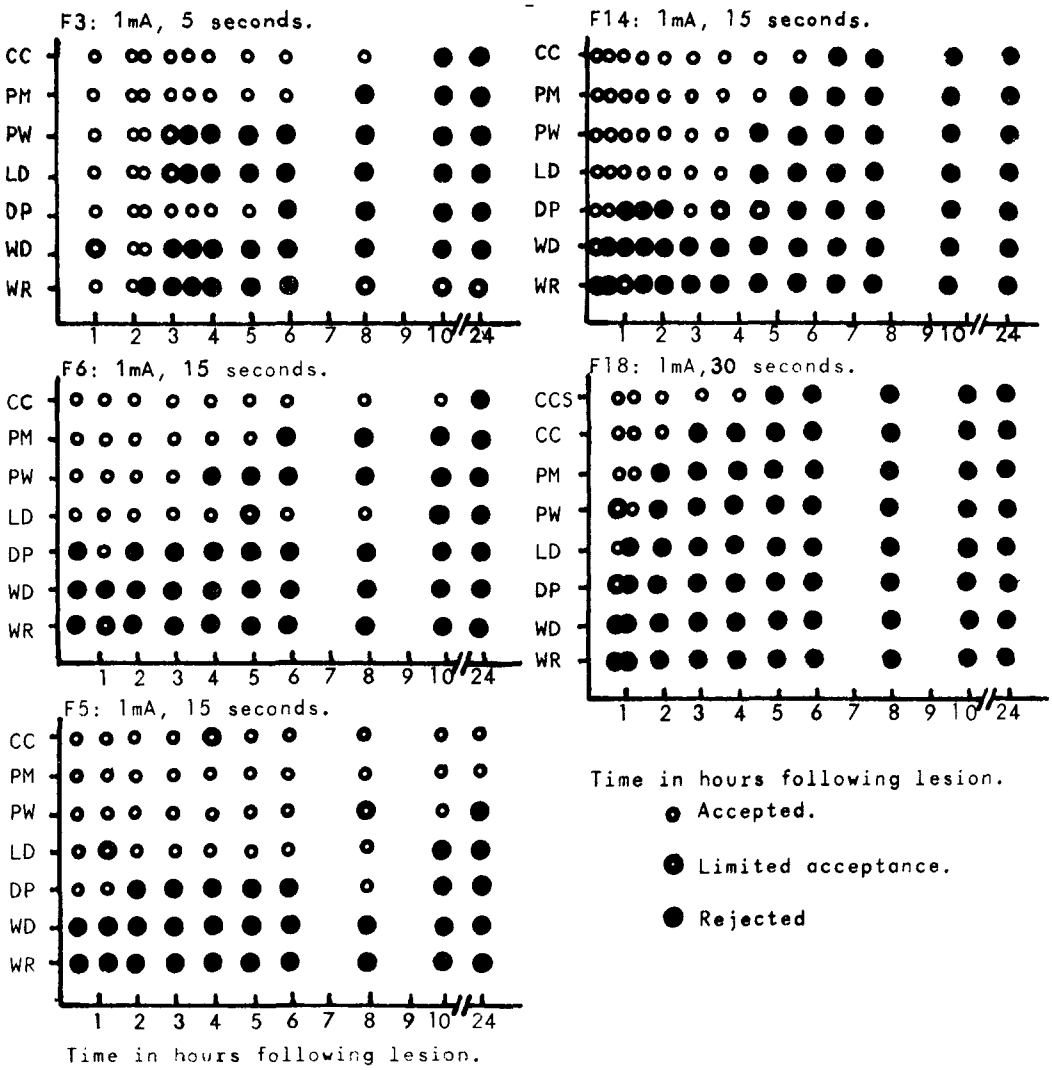

FIG. 7. Effects of bilateral hypothalamic lesions on the acceptability of water and various foods. (Animals were tested at various intervals during the day and on the subsequent day. Abbreviations: WR = water in Richter tube, WD = water in open dish, DP = dry pellets, LD = liquid diet, PW = wet Pablum, PM = moist Pablum, CC = chocolate chip cookies, CCS = chocolate chip cookies presented on spatula.

cits in drinking, for example, seemed in some cases to be associated with difficulties in licking, but in other instances, seemed more related to motivational changes. Animal F4, for example, did not drink from the Richter tube 30 min. after the lesion (15 sec., 1 ma.), but it licked water from the open dish. Immediately it pushed the dish away. It recoiled from water whenever it was subsequently presented, and on one occasion when it licked at the water dish, it immediately began rubbing its chin across the cage floor and making spreading movements with its paws.

This constellation of reactions that suggest an aversion to water may be contrasted with the deficit of Subject F3, which showed evidence of nonacceptance of both water and food based on a motor deficit. This animal would dip water from the Richter tube or open dish with its paws and bring them to its mouth. It displayed the not unusual re-

sponse of attempting to drink by inserting its lower jaw in the Richter tube opening, and ate liquid food by "chewing" at the food on the rim of its dish. Such deficits in accepting liquids (perhaps due to motor impairment of tongue movements) were shown clearly in those cases where rats continued to accept food pellets when the normally more palatable liquid diet was not accepted, or ate Pablum when it was of a drier consistency and could be bitten off in small pieces.

The progressive changes in the acceptance of food that extended over the afternoon and evening were accompanied by a number of other indications of developing behavioral abnormality. In Animal F3 the first evidence that the 5-sec. bilateral lesion was having an effect occurred after 2 hr. when it began to circle slowly about the cage, rubbing its paws and chin. This subsequently developed into an almost continuous circling with "spreading" movements of the front paws.

A number of animals either pushed pellets and food dishes away when they were offered or stepped in and spilled food. These responses almost always occurred when the animals were not accepting food or water and developed progressively during testing.

There was a general decline over time in the mobility of the animals, the vigor with which they attempted to retain pellets or food dishes, and the duration of their eating.

Recovery. The testing of recovery of drinking and feeding behavior was not complete enough to draw firm conclusions about the relation between the development of behavioral deficits and the recovery of function in individual animals. None of the lesions produced long-lasting adipsia or aphagia. Animal F8, which received the most substantial lesion and whose deficits developed most rapidly, recovered to accept palatable foods in 3 days, accepted pellets in 4 days, drank water within 6 days, and finally displayed regulatory thirst (i.e., drinking without food).

Discussion

The phenomena outlined are most directly interpretable as evidence for a local progressive deterioration of brain tissue following the production of a lesion. In the case of damage to the lateral hypothalamus, this produces a constellation of symptoms, some involving motor deficits such as problems with licking, some affecting the acceptability of water and specific food substances, and a third class including a decline in general mobility and vigor. The development of all these symptoms may be progressive when lesions are of appropriate size. It also seems reasonable to suggest that given the appropriate lesion size, location, and behavioral index, there may also be substantial immediate deficits. (A fourth class of deficits—a "sensory neglect" manifested in severe deficits in orientation to sensory stimuli—has also been shown to be produced by lateral hypothalamic damage (Marshall, Turner, & Teitelbaum, 1971). One might expect that these symptoms should also develop progressively after lesion.)

In the case of the ventromedial lesions (which were all unilateral) the deficits observed were only of one class, namely, changes in the effectiveness of electrical brain stimulation at the site of the lesion. No general behavioral deficits or changes in feeding were observed, and the deficits observed over a 24-hr. period seemed to be relatively localized, since no detectable effect could be shown in the responsiveness to electrical stimulation of tissue in the contralateral ventromedial area.

The principal theoretical interest of these observations is in the possibilities they open up for the analysis of behavioral mechanisms. In the case of lateral hypothalamic lesions there is a clear general parallel between the order in which deficits develop after damage and the corresponding opposite order in which recovery occurs; but it is equally clear that the order of development of the behavioral deficits is not always identical, opening up the possibility that phenomena such as the lateral hypothalamic syndrome may be analyzed into components on the basis of consistent variations in the time course of their appearance after damage as well as their recovery. Furthermore, the effects appear to be sufficiently local and

specific so that dynamic interrelations between one brain structure and its neighbors might be quickly assayed, either physiologically or behaviorally, following judiciously administered lesions that produce deficits progressively over time.

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