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Somnolence, akinesia, and sensory activation of motivated behavior in the lateral hypothalamic syndrome

(catalepsy/aphagia/sensory neglect/automatisms)

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ABSTRACT **After lateral hypothalamic damage in rats, somnolence, akinesia, and sensory neglect combine to produce complete aphagia. Only simple automatisms (such as grooming, chewing, licking) are present, but intense stimuli can activate more complex actions (walking, orientation, swimming). In the anorexic stage, tactile stimuli dominate in steering locomotion and "spontaneous" locomotion depends on activation from the empty stomach.**

After severe bilateral damage in the region of the lateral hypothalamus, rats stop eating and drinking and die of inanition (1). However, if they are kept alive by tube-feeding, they eventually recover (2, 3). They progress through a series of stages of control of the regulation of food and water intake that parallels the development of such controls in infancy (4, 5). In much of the work on this phenomenon, attention has focussed on the deficits in the regulation of food and water intake and body weight, particularly as evident in the later stages of recovery (Stages III and IV) (6–11). However, in Stage I (aphagia and adipsia: a complete refusal to eat or drink anything), and in Stage II (anorexia and adipsia: the animal eats some wet palatable foods but not enough to maintain its weight, and still does not drink water), the exact nature of the deficit is still very poorly understood (12–15). Recently, therefore, we have concentrated on the symptoms seen during these early stages of post-operative recovery. Thus, the phenomenon of "sensory neglect" has been demonstrated to contribute to the aphagia and adipsia seen in Stage I of the lateral hypothalamic syndrome (16–18). In the present paper, we begin a behavioral analysis of the somnolence and akinesia which are particularly evident in the first few days after such damage. These deficits combine with sensory neglect to produce complete aphagia. Then as recovery progresses to Stage II, we show how they interact when the animal is anorexic.

MATERIALS AND METHODS

Twenty-three Long-Evans hooded rats were used, 9 males (median weight: 326 g), and 14 females (median weight: 290 g). All rats were housed individually. Under Equithesin anesthesia, bilateral or unilateral hypothalamic lesions were produced by passing 1 mA of direct current typically for 20–25 sec through a stainless steel anodal electrode. The electrodes were extra-fine dental broaches with smooth shanks coated with Formvar varnish and bared to a 0.5 mm long conical tip. The stereotaxic coordinates, with skull level in the stereotaxic instrument were: 2.0 mm lateral to the midline sinus, 6.0 mm anterior to the interaural line, and 8.0 mm ventral to the dura of the cortex. We observed 18 of these operated animals for the first 7 hr after the operation to evaluate initial deficits. Then, during the early stages of recovery, neurological tests were conducted daily until some eating was seen, and less frequently thereafter. Selected samples of behavior were recorded on videotape throughout recovery. The neurological tests were designed to assess reflexive and spontaneous movements, posture, wakefulness, orientation to stimuli, and ingestion. The tests for sensory orientation were (*a*) visual: a white paper stimulus (see Fig. 2A), 5 cm in diameter with a red circle (4 cm in diameter) within it mounted on a 2 mm diameter wooden rod, was jiggled about 6 cm lateral to or above the rat's head without touching or fanning its vibrissae; (*b*) auditory: single clicks produced by a ball-point pen retractor at each side of the neck; (*c*) tactile: a light touch of the animal's fur with a cotton swab; (*d*) olfactory: a cotton swab soaked in Mennen shaving lotion or in ammonia was held about 4 cm ventrolateral to the nose. Usually a control swab (without odor) was presented simultaneously ventrolateral to the opposite nostril to insure that the stimulus controlling head orientation to the swab was odor, not sight. The other tests will be described and the number of animals to which each neurological test was applied will be specified as we report the results.

The animals fell into two groups. In seven rats which are henceforth classified with six unoperated normals as the control group the operation appeared to have little or no effect: they showed only unilateral deficits or essentially normal movements, posture, and wakefulness, and typically recovered ingestion of food and water by the first or second post-operative day. [In two of these animals, only 10 sec of current (1 mA) was passed on each side. The other five rats received unilateral lesions, which caused relatively slight unilateral deficits in orienting.] The 16 remaining operated animals (hereafter called lateral hypothalamic animals) showed behaviors typical of the lateral hypothalamic syndrome (prolonged aphagia and adipsia), along with the symptoms to be described below.

RESULTS AND DISCUSSION

Histology. The brains of six lateral hypothalamic animals were analyzed histologically. The tips of the electrodes were generally found to have been inserted at the level of the posterior portion of the ventromedial nucleus of the hypothalamus. Successful lesions typically were centered in the lateral portion of the medial forebrain bundle, resulting in bilateral destruction of at least half of each bundle. The lesions all extended anteriorly at least to the anterior portion of the ventromedial nucleus [ref. 19 (Fig. 32, A 4890μ)] and posteriorly at least to the posterior portion of the posterior nucleus of the hypothalamus [ref. 19 (Fig. 40, A 3290μ)]. The lesions generally extended laterally to involve the medial margin of the internal capsule, and also ventrally toward the dorsal border of the optic tract. In all lateral hypothalamic animals,

Abbreviation: EEG, electroencephalogram.

the nigrostriatal bundle (traversing the dorsal lateral aspect of the lateral hypothalamus) was completely interrupted bilaterally [ref. 19 (Fig. 33, A 4620μ)]. Moreover, all lesions bilaterally involved the ventral zona incerta [ref. 19 (at the level indicated in Fig. 38, A 3750μ)], thus damaging at least some of the trigeminal axons passing through the ventral collateral of the trigeminal lemniscus as it courses anteriorly. Thus, destruction of both pathways may contribute to the lateral hypothalamic syndrome (20, 21).

Behavioral Analysis. As they recovered from the anesthesia (about 1 hr following receipt of the lesions), 10 lateral hypothalamic animals displayed unusual hyperactivity characterized by stereotyped repetitive motor automatisms. The movements typically included extreme continuous dorsiflexion of the head, jumping, and obstinate progression by walking or running in a circle. Four reared upright without leaning on a wall and swivelled the upper parts of their body (head, shoulders, forelimbs, and upper trunk down to the hips) to one or both sides while displaying a repetitive pedalling movement of the forelegs. The hyperactivity typically was seen from the end of the first through the fifth postoperative hour (median duration: 4 hr; range: 2–7 hr). It gradually increased in tempo and amplitude for about 3 hr, and then subsided. Three animals remained unconscious and no observations were made on the remaining three. None of the control rats exhibited such behavior. Because the movements seen during this initial hyperactivity were then absent for some days afterward, we assume that they were produced by an initial irritative effect of the lesion (22) or a massive release of neurotransmitter from the dying cells (23, 24). Whishaw and Robinson (25) also report such hyperactivity and relate it to the irritation produced by deposition of metallic ions.

Immediately following the initial hyperactivity and on into the next postoperative day, 15 of the 16 lateral hypothalamic animals were in a somnolent stupor from which they could be roused only momentarily by sufficiently intense stimuli, such as a tail pinch. When the stimulus stopped, the animals would return to "sleep." Because no electroencephalogram (EEG) or electromyogram (EMG) measures were taken, we tentatively use the term "sleep" throughout this paper to describe animals lying prone with eyes closed, with head and limbs relaxed, and showing phasic limb extension and body startle if roused by an external stimulus. Similarly, without electroencephalographic measures, it was difficult to define a state of akinesia independent of somnolence. However, in agreement with McGinty (26), we believe that as recovery progressed, such a state existed. When such an animal, which had still not yet recovered the ability to walk spontaneously, was found standing with its eyes open in a semi-crouched posture, we characterized it as "akinetic." For the most part, this early state (which lasted as long as 6 days in one of the animals) can be described as a mixed condition of somnolence and akinesia during which the animal shows no spontaneous locomotion.

As was mentioned earlier, during this stage of complete aphagia and adipsia, all lateral hypothalamic animals displayed bilateral sensory neglect (16–18). Unlike normal rats, they did not respond to visual, olfactory, auditory, or somatosensory stimulation (touch of whiskers, skin of head, body, and limbs) by orienting the head toward the stimulus. The stimuli were effective in producing respiratory changes and other stereotyped motor automatisms (eye-closure, ear-twitching, chewing in space, tooth-grinding, chattering, or clicking, scratching with hind paw, shake or vague upward movements of the head). However, well-guided head orientation towards the stimuli was not seen during this period.

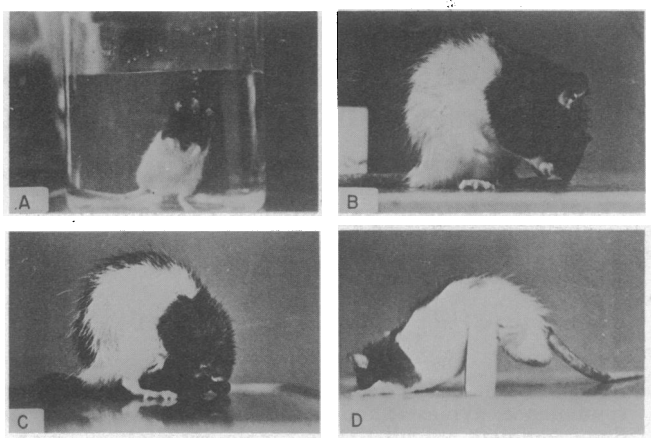

FIG. 1. Posture and movement in rats with bilateral lateral hypothalamic lesions. (A) In warm water, rat swims little or not at all. Cycle of exhalation under water as in photograph, followed by thrust against bottom of tank with rear leg propelling rat to surface for inhalation may be observed. (B) "Frozen" stance following short period of grooming. (C) Gradual subsiding follows "freezing" and sometimes leads to top of head resting on table tucked between forelegs. (D) Rat remains in cataleptic awkward posture for indefinite period.

Grooming appeared to be the only "spontaneous" complex behavior pattern remaining. On the first postoperative day, five animals groomed both head and some part of the body; eight groomed only the head (grooming observations were not made on the other three). It was quite striking to see an apparently immobile animal, totally devoid of such spontaneous actions as walking or orientation, suddenly rear up into a grooming posture, go through a brief sequence of wiping the head and snout with its forepaws, then turn its head to lick at the body fur both lateral and ventral, at the end of which it slumped back into virtually total immobility (see Fig. 1B). It was as though simple stereotyped automatisms were available for reaction to internal or external stimuli, but more "complex" (self-initiated or self-guided) patterns, such as those involved in orientation or walking, were not. Similar behavioral dissociations in rats with posterior hypothalamic damage have been reported by T. E. Robinson and I. Q. Whishaw (27). As will be discussed below, these two categories of action pattern correspond very closely to those described by Vanderwolf as being associated with two distinct patterns of hippocampal EEG rhythm (28, 29).

The somnolence and immobility which characterized the stage of aphagia and adipsia seemed to be caused by a persistent lack of tonic arousal, perhaps related to damage to the reticular activating system which runs through the lateral hypothalamus (30). Thus, intense stimuli could momentarily activate some behavior patterns that would not otherwise appear. For example, if a normal adult rat is placed in a tank of water (temperature 33°C or 23°C), it swims vigorously to the side of the tank, using hind leg kicks to propel it, while keeping its nose well above the surface and planing with its forelegs held immobile in front of it (31) and climbs out. As shown in Fig. 1A, in water at 33°C (to our touch, this felt neither warm nor cool), lateral hypothalamic animals sank to the bottom, not swimming at all, or kicking upward only intermittently or very slowly (in six of seven tested; the seventh swam actively, but its head remained underwater). However, when the water was colder (23°C), they all swam

vigorously with nose well above the surface. In one very striking instance, when dropped into cool water, an otherwise profoundly akinetic rat swam rapidly to the side of the tank, climbed up on the edge, leaped 1.5 m to the floor, ran a quarter meter and then lapsed into complete immobility once again. Similarly, though orientation to other stimuli was absent on the first postoperative day, a clear orienting movement of the head could be elicited by firmly grasping a paw with a pair of forceps. (Thirteen animals oriented toward at least one paw and 11 of these actually touched the forceps with their snout or bit them.) Such phenomena suggest that the lack of availability of complex action patterns seen in these animals may be due, at least in part, to deficits in a tonic activating system that is necessary to maintain the normal spontaneity of motivated behavior.

Robinson and Whishaw (27) and Robinson, Whishaw and Wishart (32) report a similar phenomenon in rats with posterior hypothalamic damage. Indeed, such rats groom under warm water while sitting on the floor of the tank, not swimming even though they are in serious danger of drowning. In our lateral hypothalamic damaged animals, we observed a few swipes of the head with the forepaws underwater, but no coordinated grooming. In general, however, our observations and interpretations of the behavior of rats with lateral hypothalamic damage closely resemble theirs, and suggest the involvement of a common neural activating system.

Sudden somnolence was another manifestation of the lack of tonic activation. For the first few postoperative days (median: 4 days; range: two to seven) in all 13 animals observed, grooming bouts lasting only seconds were typically terminated in mid-groom by a sudden arrest of all movements (Fig. 1B). Then, over several minutes, the head slowly sank downward until it touched the table, and often slid under the body between the extended forelegs with the top of the head resting on the table (Fig. 1C). The body would then also gradually relax. A few days later in recovery, such an animal's head would start to sink after an arrest of grooming, but before it sank far, another short bout of grooming would occur. In this manner, several groom-arrest cycles would typically occur before the rat subsided into sleep. Neither control nor normal rats ever showed this phenomenon of groom-arrest by somnolence.

Deficits in activation also seemed to contribute to the cataleptic postures which such animals adopted or into which they could be placed (13, 33). They would display a "forgotten limb," in which the experimenter would pull a leg out laterally, or, accompanying a spontaneous movement of the head or trunk, a leg would be stretched out laterally. Then instead of being retracted to a normal position, the leg remained splayed out awkwardly for a long period of time (seen in nine of 11 lateral hypothalamic rats observed). Similarly, all such animals failed to extricate themselves when propped up over a block of wood (6 cm high by 2 cm thick) placed under their chest or abdomen (Fig. 1D), when placed with head hanging down over the edge of a table (seen in eight of 10 observed) or when suspended by their teeth from a swab stick (five failed; four escaped within 3–29 sec; one escaped within 2 sec as did all controls). Such failures to adjust their posture did not seem to be due to total inability to move the limbs or body. Thus, flexion reflex withdrawal of the limbs could be elicited by a pin prick of the paw or pinch by forceps. Similarly, they would right themselves reflexively from a supine position and would lean in a compensatory fashion on a tilt-table to remain upright.

As recovery progressed, head orientation to whisker touch and olfactory stimulation returned (16, 17). Associated with such head orientation was locomotion with the forelimbs. This resulted in movement of the head and upper trunk toward these stimuli. At first, the hind limbs did not participate in locomotion. The animal would be rooted in one place in the cage on its haunches and hind limbs, but it would make orienting and forelimb locomotion approach movements of head and upper trunk toward stimuli in front or to the side.

The combination of forelimb locomotion and head orientation to smell and whisker touch appears to be necessary for the transition from Stage I to Stage II (aphagia to anorexia) in the lateral hypothalamic syndrome (16, 17). Eight lateral hypothalamic animals recovered the three functions of ingestion, spontaneous forelimb locomotion, and orientation to olfactory stimuli. Seven started eating on the same day or 1 day after orientation to olfactory stimuli and spontaneous forelimb locomotion were both first seen. In the remaining animal, eating was seen 3 days after orientation and forelimb locomotion jointly recovered. (In this case, we believe the recovery of ingestion was complicated and delayed by a motor impairment in tongue protrusion which, if it occurs in other animals, is so transient that it usually disappears before the recovery of head orientation. Four other animals recovered to the stage of anorexia, but they were so hyperactive that olfactory orientation could not be tested adequately.)

With further recovery, active forward progression, involving all four legs in at least three successive steps, was seen in all animals ($N = 13$) from 3 to 10 days postoperatively (median: 6 days). To the casual observer, these lateral hypothalamic animals seemed relatively normal when forward progression had returned. Thus, when such a recovering animal was placed on a table, it would engage in what appeared to be spontaneous exploration, and if crumbs of food were encountered, might actively nibble at them. However, close observation revealed a number of residual deficits, both in the character of its exploratory movements and in the nature of the stimuli that controlled them. For instance, their movements were extraordinarily stereotyped, consisting of relatively few movement patterns. This was particularly clear when in the course of random walking on the table top they walked into a corner formed by the junction of two walls. A normal animal would rear and turn away, or simply turn 90°–120° in a smooth movement, and walk in another direction. In contrast, the movements of the recovering lateral hypothalamic animals were so limited that they sometimes appeared to be trapped in the corner for long periods (seen in four rats). On encountering the corner with its snout, such an animal would tuck its head about 2 cm backwards in a ventral movement and take a step backward with its forelegs. Then it would swing its head forward at an angle of about 30° to left or right and take a step forward with its foreleg. This movement was not sufficient for the animal to disengage from the corner, so its head would bump the other wall, tuck backward, and then swing forward to the other side, once again encountering the original wall. This cycle could repeat itself 10 or 12 times, with the withdrawal movements gradually increasing in amplitude until one finally was sufficient to bring the animal clear of the corner on its next movement forward, and the animal would then once again be free to roam the area. Similar stereotyped withdrawal patterns were seen when the animal lowered its head over the edge of the table. Indeed, the withdrawal, turn, and forward progression pattern was sometimes so stereotyped as to resemble a waltz dance step.

Such "mistakes" in what otherwise appear as adaptive goal-directed locomotor approach patterns suggest that the behavior patterns seen in the early stages of recovery are more reflexive (organized at a lower level of nervous function) than is characteristic of normal motivated behavior.

In addition, at this stage (usually early in Stage II), the animal's behavior depended to an extraordinary degree on very specific external stimuli. For instance, despite the fact that these animals could obviously see [visual neglect had by this time disappeared, and they would orient their heads (Fig. 2A) or rear upwards to a moving visual stimulus; seen in 10 lateral hypothalamic rats], their "spontaneous" exploratory activity seemed to be totally steered by tactile stimuli. As shown in Fig. 2B, such an animal typically kept its chin less than 1 cm above the surface of the table as it walked. One might think this due to a postural impairment in head and/or upper trunk fixation (34), but if the animal encountered a vertical surface of an object or the wall of its cage, its head and trunk often moved smoothly upwards in what appeared to be a tactile scanning exploratory movement. Similarly, if it came to the edge of the table, its chin moved along the table surface and downwards over the edge in close contact with the vertical surface. All 13 rats recovering spontaneous locomotion showed this behavior. Normal and operated control animals sometimes also explored with chin held low, but frequently raised their head to shoulder level or spontaneously reared up on their hind legs (Fig. 2C) while seeming to look spontaneously at objects (like furniture or equipment) near the testing table. When they came to the edge of the table, they would extend their heads out into space (rather than downwards) looking first outward and only then would they explore the vertical surface downwards. It appears, therefore, that in recovery from the visual sensory neglect produced by lateral hypothalamic damage, a transition stage in the visual control of exploratory activity can be isolated. During this period, the recovering animal orients and rears upward "reflexively" to moving visual stimuli (Fig. 2A), but unlike the normal animal, does not yet possess the apparently more complex form of visual control involved in self-initiated "looking" at stationary objects. This visual defect also apparently affected the animal's ability to find and eat food. For instance (in all five rats tested), if the food were presented on the surface of the table in a clear glass dish (6 cm in diameter with vertical sides 2 cm high), the animal's snout, during its tactile sweep of the surface, would often encounter the dish and sweep right on past the food, or around the wall of the dish. Only occasionally would a vertical sweep of the animal's snout upward bring it into contact with the food, with the result that nibbling would ensue. Similarly, while the animal was nibbling at the food in the dish, or even at a pellet on the table top, if the dish or pellet were moved a couple of centimeters away, the animal ignored or seemed to lose it and renewed its seemingly randomly directed tactile exploration of the surface. Thus, it appears that exploratory locomotion and orientation to food during the stage of anorexia is reflexive, rather than self-directed. It is possible that the ability to search in a directed manner for food is necessary for the transition to Stage III, where caloric regulation occurs; but this requires more systematic documentation.

Finally, like normal animals, these recovering lateral hypothalamic animals explored in a hyperactive fashion when they had not been fed for several hours. However, their "hunger drive" still seemed abnormal. If they were tube-fed 10–15 cc of a liquid diet, they lapsed into the state of immobility and extreme unresponsiveness to external stimuli characteristic of the early postoperative period of somnolence and akinesia. All seven animals tested during Stage II became immobile. Five of these were also very unresponsive. Normal animals were somewhat sluggish after tube-feeding, but never to such a marked degree. For instance, a tube-fed recovering lateral animal often remained almost totally limp and unresponsive while suspended head downwards by its tail (Fig. 2D), a state never seen in normals. It was as though the spontaneous activity of recovering lateral animals in this early stage (anorexia) was mainly "gastrically driven"—i.e., when the level of endogenous activity of the damaged reticular activating system is still low, internal control of hunger arousal and "motivation" appears to depend almost completely on stimuli arising from the empty stomach. Alternatively, one may view such torpor as an exaggerated susceptibility to inhibition of motility by gastric fullness. In some ways, this resembles a phenomenon seen in the normal neonate, where control of waking and activity depends largely on the state of fullness of the stomach (35). A similar phenomenon has been found in thalamic and decorticate rats (36, 37).

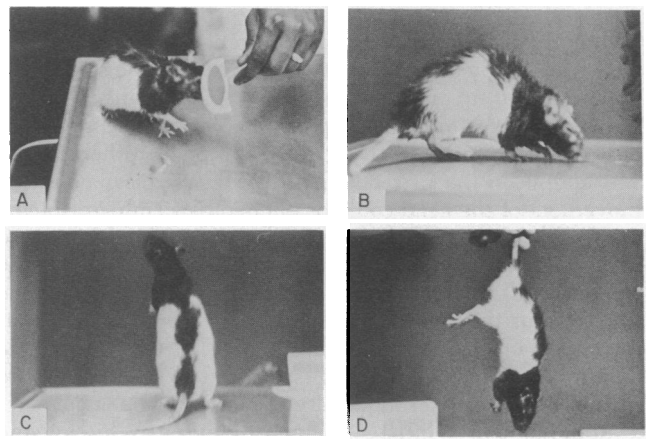

FIG. 2. Recovering lateral hypothalamic and normal rats. (A) Recovering rat raises head from table in orienting to moving visual target. (B) During active spontaneous locomotion, recovering rat is guided by tactile snout contact. (C) Normal rat spontaneously rears high with no nearby moving target eliciting movement. (D) Recovering rat that eats and walks when its stomach is empty becomes inert and unresponsive (here it hangs limply when suspended by the tail) shortly after tube-feeding.

In summary, bilateral damage in the region of the lateral hypothalamus produces somnolence, akinesia and sensory neglect. These phenomena contribute to the complete aphagia and adipsia seen in the first stage of the lateral hypothalamic syndrome. In this early period, only stereotyped automatisms such as chewing, licking, and grooming are present. These automatisms correspond closely to the patterns of behavior Vanderwolf and Whishaw (28, 29) have shown to be associated with one form of hippocampal EEG rhythm—large amplitude, irregular activity. Such patterns (like grooming) appear to represent rather simple centrally programmed fixed action patterns which are relatively independent of re-afferent feedback (38). Intense stimuli such as pain and cold can produce the increased activation which is necessary for more complex behavior such as walking, orienting, or swimming. As recovery progresses, these patterns reappear. It has been suggested by others (28, 29) that they are related to another type of EEG rhythm—hippocampal theta. During the anorexic stage, specific external stimuli

(tactile stimulation of whiskers and snout) appear to predominate in the reflexive steering of spontaneous locomotion and orientation to food, and hunger drive appears to depend largely upon the activation provided by stimuli arising from the empty stomach. Thus, in the stages of recovery characteristic of the lateral hypothalamic syndrome, we may have a useful experimental model for isolation and re-integration of simpler behavioral and EEG components of motivated activity, differing in the complexity of their control mechanisms and hierarchically represented in the nervous system (39).

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