Effects of brainstem lesions on temperature regulation in hot and cold environments

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LIPTON, J. M., P. E. DWYER, AND D. E. FOSSLER. Effects of brainstem lesions on temperature regulation in hot and cold environments. Am. J. Physiol. 226(6): 1356-1365. 1974.—Rectal temperatures (T_r) of rats with electrolytic lesions or knife cuts in the brainstem were recorded during 7-h exposures to 5 and 35°C. Rats in which the preoptic/anterior hypothalamic (PO/AH) region was destroyed or disconnected from neighboring tissue showed disturbances in regulation against both heat and cold. Animals with medial cuts which precisely separated the PO and AH nuclei showed thermoregulatory deficits in the high or in the low ambient temperatures, but not in both. Similar medial cuts rostral and caudal to the PO/AH junction had no effect on thermoregulation. Bilateral parasagittal cuts between the PO/AH region and the lateral hypothalamus caused T_r to fall in the cold. Cuts bordering the PO/AH region at its anterior, posterior, and dorsal limits and other cuts which severed connections in mid and posterior hypothalamus, the tegmentum, and the central gray matter did not influence T_r in the extreme environmental temperatures. Lesions in the medulla oblongata at sites known to be thermosensitive produced deficits in resistance to either overheating or chilling. The results show that the integrity of the PO/AH junction and of the thermosensitive region of the medulla oblongata is necessary to regulation of body temperature. Because the lateral parasagittal cuts disturbed regulation against cold and only total isolation of the PO/AH region disturbed regulation against heat, it is concluded that the cold pathways pass laterally from the PO/AH junction while the heat pathways are redundant at this level.

MATERIAL AND METHODS

The general approach was to produce lesions or knife cuts in selected regions of the brainstem in adult male albino rats (300 g) and to compare the resulting changes in body temperature during exposure to high and low ambient temperatures with those observed using sham-operated control animals. Brain lesions, cuts, or control procedures were carried out using 586 rats in these experiments. Because it was impossible to locate accurately the extremely narrow knife cuts in the brains of some rats and other rats died after the surgery or showed signs of inani-

Two types of wire knives were used to make cuts in the brainstem. To cut off all connections between the PO/AH region and neighboring tissue, a knife similar in design to that described by Halász and Pupp (16) was used. In order to reduce the amount of tissue destroyed, the knife was modified to use a .005 inch diam tungsten wire for the cutting portions of the knife assembly. Pilot work showed that, to assure complete disconnection of the PO/AH region from surrounding tissue, the horizontal zero plane had to be altered by lowering the incisor bar 15°. The se-
and type of knife was similar to that described by Sclafani and Grossman (49). This knife was made of 30-gauge stainless steel tubing bent at the tip so that a .005-inch diam tungsten wire could be extended from it laterally by sliding the wire through the lumen. In order to make the cuts more precise, each of the knives of this type were photographed with from 1 to 4 mm of the wire blade exposed. Photographic negatives enlarged to correspond to the dimensions of the de Groot (15) stereotaxic atlas of the rat brain were used to determine at what point in the brain the knife should be extended, where the cut should stop, etc., in order to sever specific connections. To facilitate cutting of large fiber bundles, both types of wire knives were sharpened under a microscope.

After the experiments were completed, the animals were killed with an overdose of sodium pentobarbital, and the brains were used to determine at what point in the brain the knife should be extended, where the cut should stop, etc., in order to sever specific connections. To facilitate cutting of large fiber bundles, both types of wire knives were sharpened under a microscope.

Rectal temperatures were measured every 0.5 h for the first 2 h, and then every hour for the remainder of the 7-h experiment. Animals were removed from the chamber and artificially cooled or warmed if rectal temperature rose above 41-42°C or fell below 34°C, respectively. The second of the two exposures was performed 3 days later.

Because these experiments took place over a 2-yr period and involved several shipments of rats, it was necessary to compare results obtained using the animals with brainstem lesions with those obtained using control animals drawn from the same shipment. Decisions as to whether specific lesions produced deficits in thermoregulation were made by comparing graphic T, records of animals with PO/AH region lesions in the heat and in cold (Fig. 1, Table 1). Animals with less damage to the PO/AH region showed an elevated heat dissipation threshold and low body temperatures at levels comparable to those seen in the control animals. Rather, their body temperatures stabilized at around 40.5°C in the heat and about 36.5°C in the cold. Rectal temperatures obtained in the same experiments on control rats and 10 additional animals with lesions that were posterior to the PO/AH region stabilized at 38-39°C in the heat and at 37.5-38.5°C in the cold. The results on animals with subtotal PO/AH destruction are similar to those obtained by Keller and his co-workers (23, 24) and by Anderson et al. (1) who found that PO/AH lesions caused a permanently raised heat-dissipation threshold and an impaired regulation against cold.

**RESULTS AND DISCUSSION**

**PO/AH lesions.** Destructive lesions in the PO/AH region caused decreased ability to maintain normal body temperature in the heat and in the cold (Fig. 1, Table 1). Large lesions that destroyed the medial preoptic region and much of the anterior hypothalamic tissue caused the greatest deficits. Six of the animals with large lesions showed no regulation against cold and had to be removed from the chamber early in the experiments in order to keep them alive, whereas four of the same animals showed dangerously high body temperatures in the heat. Four other rats with less damage to the PO/AH region were able to regulate against the high and low ambient temperatures, although they could not maintain their body temperatures at levels comparable to those seen in the control animals. Rather, their body temperatures stabilized at around 40.5°C in the heat and about 36.5°C in the cold. Rectal temperatures obtained in the same experiments on control rats and 10 additional animals with lesions that were posterior to the PO/AH region stabilized at 38-39°C in the heat and at 37.5-38.5°C in the cold. The results on animals with subtotal PO/AH destruction are similar to those obtained by Keller and his co-workers (23, 24) and by Anderson et al. (1) who found that PO/AH lesions caused a permanently raised heat-dissipation threshold and an impaired regulation against cold.
The PO/AH lesions also altered body temperature in a thermoneutral (23°C) environment (Fig. 2). As in previous studies (30) body temperatures showed a net rise after major injury to the PO/AH region. The net increase was marked by large variations throughout the postoperative period. The increase in $T_r$ and the variability in daily $T_r$ measures were less marked in rats with small PO/AH lesions. An increase in the variability of daily rectal temperatures of cats with lesions in the medial preoptic region has also been reported by Squires and Jacobson (44).

These findings support earlier reports that PO/AH injury results in defective thermoregulation (37 and others). However, unlike early research on cats and monkeys (39, 46), PO/AH lesions were found to reduce the ability to regulate against cold as well as heat. The findings also support the concept of a secondary central temperature control (9, 10, 31), since the regulation of body temper-

### Table 1. Effects of electrolytic lesions and knife cuts on rectal temperature in heat and in cold

<table>
<thead>
<tr>
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<th>5°C Environment</th>
<th>35°C Environment</th>
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<tr>
<td></td>
<td>Initial tempera-</td>
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<td>Cuts and lesions that disturbed thermoregulation</td>
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<tr>
<td>PO/AH lesions</td>
<td>10 39.7 ± 0.2</td>
<td>-4.3 ± 0.5</td>
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<tr>
<td>PO/AH junction cuts</td>
<td>10 36.0 ± 0.7</td>
<td>-3.8 ± 0.4</td>
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<td>PO/AH disconnections</td>
<td>9 38.7 ± 0.1</td>
<td>-3.7 ± 0.4</td>
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<tr>
<td>Parasagittal cuts</td>
<td>5 38.5 ± 0.3</td>
<td>-1.9 ± 0.5</td>
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<td>Medullary lesions</td>
<td>4 37.0 ± 0.4</td>
<td>-2.8 ± 0.6</td>
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<tr>
<td></td>
<td>4 37.0 ± 0.4</td>
<td>-2.8 ± 0.6</td>
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<tr>
<td>Cuts and lesions that did not disturb thermoregulation</td>
<td>131 37.9 ± 0.3</td>
<td>-4.3 ± 0.5</td>
</tr>
<tr>
<td>Controls</td>
<td>73 37.8 ± 0.1</td>
<td>-0.2 ± 0.3</td>
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Temperature values are means ± SE. * Not the same animals that showed deficits in the cold.

FIG. 2. Variations in body temperature in a single rat after large PO/AH lesions. Postsurgery body temperature remained higher than control values throughout period of measurement. Ambient temperature was 23°C. 5°C = day of test in cold environment, 35°C = day of test in hot environment.

FIG. 3. Medial cuts that damaged PO/AH junction caused deficits in thermoregulation in either 5 or in 35°C environments. Brain sections show location of 2 of 17 cuts that produced thermoregulatory deficits and sites of 2 other cuts that had no effects on regulation against heat or cold. Within region of brainstem bounded by the 2 ineffective cuts shown in the figure, cuts made anterior or posterior to PO/AH junction or unilateral cuts through junction had no effect on thermoregulation ($n = 24$). Medial cuts ($n = 17$) rostral to anterior ineffective cut shown in figure, at levels up to most anterior portion of the PO nuclei, did not influence body temperature in 5, 23, or 35°C environments. Cuts made caudal to posterior ineffective cut ($n = 6$) at levels extending to mid AH region were also without effect on body temperature in hot, cold, and neutral environments. All cuts that caused thermoregulatory deficits involved medial 2.5–4.0 mm of brainstem.
temperature in the 23°C environment was not totally abolished by destruction of the PO/AH region.

Medial cuts within PO/AH region. Medial cuts that separated the preoptic from the anterior hypothalamic nuclei caused disturbances in regulation against cold in 10 rats and against heat in others, but never markedly disturbed both types of regulation in the same animal (Fig. 3, Table 1). Among the 10 rats that showed thermoregulatory deficits in the cold, T_r dropped 2.1-6.5°C and 5 animals had to be removed from the chamber to prevent fatal hypothermia. Three of the seven rats that showed thermoregulatory deficits in the heat were removed after T_r increased 2.7-3.6°C. There was also considerable disturbance in resting body temperature among the 10 animals. Both abnormally high (e.g., 40°C) and abnormally low (e.g., 31.1°C) T_r's were recorded in these rats.

A careful histological study by independent judges indicated that the cuts which produced marked deficits in regulation against cold were slightly posterior to the cuts in the rats that had difficulty regulating T_r in the 35°C environment. The placement of the cuts was of extreme importance because sections made even slightly more anterior or posterior to the junction of the nuclei or which spared the junction unilaterally had no significant effect on body temperature in the 5 and 35°C environments. Medial cuts made at other points in the PO/AH region or through the anterior border of the preoptic nuclei also had no marked effect on body temperature. Keller (24) and other investigators (13, 39, 46) concluded from their experiments that it was possible to separate independent nervous mechanisms responsible for regulation against heat and cold by gross lesions and brainstem transections. The results of the present experiments indicate that it is possible to separate the mechanisms, within the primary temperature control region, by making medial cuts which destroy very little brain tissue. It appears from the marked differences in the thermoregulatory deficits produced that the neural connections subserving heat and cold regulation, although very closely arranged, are separate within the PO/AH junction.

The results indicate that the connections between the preoptic and the anterior hypothalamic nuclei are of considerable importance to normal regulation against extreme environmental temperatures. The results further suggest that, except for the tissue in the immediate region of the PO/AH junction, the integrity of connections with more anterior or posterior portions of the nuclei is not required to maintain normal temperature in the heat and cold. Also, the failure of the cuts which separated the preoptic nuclei from anterior telencephalic structures to alter temperature regulation is consistent with the idea that the cerebral hemispheres and other structures above the PO/AH region are not required for thermoregulatory responses to occur (4, 5, 26, 33, 38, 41, 45).

PO/AH disconnections. Taking great care not to disturb the blood supply to the base of the brain, a knife was rotated 360° so as to produc a cylinder of tissue approximately 2 mm high and 3 mm in diameter which contained the PO/AH region (Fig. 4). These cuts typically involved the anterior portion of the preoptic nuclei, the diagonal band of Broca, the lateral portion of the preoptic region, and the mid and posterior portions of the anterior hypothalamic region. Dorsally, the anterior commissure was encroached upon in four rats. Cutting off communications between the PO/AH region and neighboring structures in this way caused disturbances in temperature regulation in
FIG. 5. Effects of bilateral parasagittal cuts that completely separate PO/AH region from its lateral connections in a single animal. These cuts produced deficits in regulation against cold but not against heat. Brain section shows location of 1 of the cuts at approximately 1.3 mm lateral from midsagittal plane.

Lateral parasagittal cuts. The parasagittal cuts were designed to sever connections between the PO/AH region and the lateral hypothalamic structures on either side. In all animals the cuts were made 1.3–1.5 mm on each side of the midline and extended from points anterior to the PO nuclei to the fornix. The cuts involved the lateral preoptic region, the diagonal band of Broca, the lateral portion of the anterior hypothalamic nuclei, and portions of the fornix. Five of the 10 rats with lateral parasagittal cuts could not maintain their body temperature at normal levels in the cold and showed decreases in \( T_r \) as great as 2.9°C (Fig. 5, Table 1). However, the thermoregulatory deficits were not great enough to cause the temperatures of the animals to drop to dangerous levels within the 7-h period. None of the animals had difficulty regulating against heat or showed any disturbance in normal resting temperature. A significant portion of the pathways that are important to regulation against cold are believed to course laterally near the ventral surface of the brain, since cuts which did not extend to the base of the brain also did not influence regulation in the 5°C environment. These results indicate that at least a part of the results obtained when the PO/AH region was disconnected, namely the deficits in regulation against cold, may be attributed to the severing of connections with the medial forebrain bundle (MFB) and lateral hypothalamic regions. From the present data, it seems not unreasonable to assume that afferent or efferent pathways necessary for regulation against cold run from the PO/AH junction laterally to the MFB and from there descend to effectors and/or temperature receptors.

Horizontal cuts above PO/AH region and cuts through stria terminalis. Connections with the thalamus and other structures above the PO/AH region were severed by lowering the knife assembly, 1.5 mm on either side of the midline, to a point anteroventral to the anterior commissure, extending the wire blade 3 mm, and turning the assembly 90° so that the blade moved from a medial plane to a parasagittal plane. This procedure produced two overlapping cuts which extended over the medial preoptic region, the
anterior hypothalamic nuclei, and the periventricular nuclei (Fig. 6). These cuts did not influence body temperature in either the 5 or the 35°C environments in 16 rats (mean maximum ΔT: in 5°C = −0.1°C; in 35°C = 1.6°C) when these temperature records were compared with those of eight control animals tested on the same days or with those of control animals in other experiments in the series.

Electrical stimulation of the basal amygdaloid nucleus produces a fall in rectal temperature when the ambient temperature is high (21). Further, destruction of the basal amygdaloid nuclei causes a reduction in the influence of skin temperature on respiration rate (22). From these results it would appear that the basal amygdala might play an important role in regulation against heat by altering the significance of peripheral temperature to thermoregulatory responses. Since most efferent fibers of the basolateral amygdala are carried in the stria terminalis which passes medially to reach the medial preoptic region (14), it might be expected that disruption of the stria terminalis would disturb body temperature regulation in the heat. However, when the stria terminalis was sectioned bilaterally at a point slightly posterior to the anterior commissure (Fig. 6) in 14 rats, no disturbances in regulation against heat or cold or resting body temperature were seen. These findings indicate that the amygdala does not influence body temperature through signals carried by the stria terminalis, but they do not exclude the possibility that diffuse ventral amygdalofugal pathways (35) might carry information important to thermoregulation to the PO/AH region. It is interesting to note that these ventral pathways were probably severed in the animals with lateral parasagittal cuts that showed defects in regulation against cold.

Medial cuts in mid and posterior hypothalamus, tegmentum, and central gray. None of the transverse cuts through the hypothalamus below the anterior hypothalamic region (Fig. 7) markedly influenced the resistance to chilling or overheating. The only abnormality seen was a slight reduction in resting body temperature of animals with cuts immediately anterior to the posterior hypothalamic nuclei. However, the body temperatures of these animals were normal after the first 0.5 h in the cold, and they showed no deficits in regulation against heat. The cuts in the hypothalamus interrupted periventricular and other medial interhypothalamic connections between the PO/AH region and the posterior hypothalamus in 16 rats. If, as recently suggested (18, 36, 48), the posterior hypothalamus integrates afferent information from the PO/AH and other thermosensitive regions and organizes effector activity, then the communication channels between the anterior and posterior regions must be laterally placed. There is evidence (41) that the posterior hypothalamic nucleus sends fibers to the medial forebrain bundle, but Knook (28) was unable to determine if fibers from the preoptic region also project to this nucleus in the rat. This point will be clarified if, in future experiments, parasagittal cuts lateral to the posterior hypothalamic nucleus reduce the resistance to chilling and to overheating.

The effects of interhypothalamic cuts differ considerably from those seen by researchers who made lesions in the mid and posterior hypothalamus. For example, Isen-
schmid and Schnitzler (20) made rabbits poikilothermic through caudal hypothalamic lesions, and Clark, Magoun, and Ramson (13) found that lesions in the caudal hypothalamus abolished or impaired resistance to body cooling. McCrum (34) has reported that lesions at several points in the hypothalamus of the cat alter regulation against external heating and cooling and the body temperature response to morphine injection. It may be that the results of these and other similar experiments are due to relatively greater destruction of nuclei, fibers, and tracts than that produced by the wire knives used in the present experiments.

After tegmental lesions near the red nucleus of the cat, Beaton, Leininger, and McKinley (6) observed impairment of heat-loss activity with an elevation of heat dissipation threshold and a reduction in total response. In the current experiments medial tegmental sections (Fig. 7) which cut off anterior connections of the red nucleus or severed the nucleus entirely in seven animals caused no abnormalities in the response to heat or cold. It may be that the differences in results between the present experiments and those of Beaton et al. (6) are also due to differences in the amount of tissue destroyed. However, judging from the examples provided by Beaton et al. (6), the tegmental cuts in the present experiment simply may not have interrupted more laterally coursing heat-loss fibers. There is also evidence that the pathways necessary for shivering pass immediately lateral to the red nucleus in the midbrain (7, 8, 15). This would account for the failure to observe deficits in regulation against cold after the medial tegmental cuts were made. It appears from the combined results that the mesencephalic connections necessary for protection against heat must occupy at least an intermediate if not a lateral or dorsal position.

Cutting the dorsal longitudinal bundle of Schutz, the main descending efferent pathway of the hypothalamus and the central gray substance of the midbrain also failed to influence thermoregulation in 10 rats (Fig. 7). This finding agrees with the results of Beaton et al. (6) who showed that lesions which interrupted the central gray matter and the periventricular paths in the cat preserved normal regulation against heat and cold.

Medullary lesions. Single electrolytic lesions in the medulla oblongata disturbed defense against cold in four rats (Fig. 8, Table 1). The decreases in body temperature in two of these animals were so rapid and unexpected that the animals died in spite of their early removal (60-90 min) from the cold environment. Resting body temperatures of the four animals were about 1°C lower than those of the rats with lesions that did not disturb regulation against cold. The two remaining rats that had shown poor regulation against cold were capable of defending against heat. Although their low body temperatures caused the maximum ΔT values to be large, these animals were able to regulate body temperatures at about 39.5°C.

Four other rats showed temperature records that were indicative of a late failure in regulation against heat (Fig. 8). In these animals the body temperature curves were not different from those of the controls during the first 4 h. Thereafter, body temperatures began to show progressive rises up to 41.0°C over the remainder of the 7-h test period. This temperature pattern is similar to that observed in some rats in which the PO and AII nuclei were separated (see Fig. 3). Outside of the medulla lesion experiments, tem-
temperatures over 40.1°C were seen only in the animals with PO/AH lesions, junction cuts, and disconnections.

The lesions that produced deficits in thermoregulation were found to lie below the floor of the fourth ventricle and the central canal at points in the upper and lower medulla. It was not possible to separate the animals that had deficits in regulation against cold from those that showed late failures in heat regulation on the basis of the loci of the lesions. Lesions which disrupted thermoregulation involved the vestibular nucleus, the dorsal portion of the fasciculus longitudinalis medialis, and damage to structures around the central canal, and in the reticular substance. In general, the regions destroyed represented sites within the region where thermal stimulation has been shown to influence body temperature (31). Lesions that did not disturb thermoregulation (n = 11) involved slight injury to the locus coeruleus or the vestibular nuclei alone, larger lesions extending deep into the midline to destroy much of the raphe, or lesions in the cerebellum over the fourth ventricle.

**GENERAL DISCUSSION**

The results underscore the importance of the PO/AH region and the significance of its connections with neighboring structures in temperature regulation. The finding that separation of the medial preoptic nuclei from the anterior hypothalamus produces marked deficits in resistance to overheating and overcooling is new. This is the first time that such a small anatomical portion of the PO/AH region has been definitively associated with thermoregulatory defects. Because cuts in the PO/AH junction of any single rat produced marked deficits in only one type of regulation (either against overheating or against chilling) and slight or no deficits in the other type, the neural connections which control heat production and heat loss activities must lie in close proximity within this region. If our observations are correct, then previous findings in PO/AH lesion studies which showed some animals to develop hyperthermia and others to develop hypothermia might be explained by differences in the exact locus and extent of the injury to the junction without necessarily involving the destruction of temperature-sensitive cells.

When the data from the tests after medial PO/AH cuts are put together with the results of other experiments in the present and previous research, a picture of the connections required for temperature control emerges (Fig. 9). In this scheme, communication between the preoptic and anterior hypothalamic nuclei is necessary for normal regulation against extreme environmental temperatures. That the junction itself is of prime importance is clear since, if the junction and only a small amount of PO and AH tissue are intact, no disturbances in thermoregulation are observed. Because medial cuts anterior or posterior to the junction or above it in a horizontal plane do not alter the resistance to heating and cooling, at least some of the pathways necessary for thermoregulation must course laterally. In fact, lateral parasagittal cuts that severed connections between the PO/AH region and the medial forebrain bundle and lateral hypothalamic region did disturb regulation against cold. This finding fits with data on electrolytic lesions in rats collected by Sherwood and others (43) who suggested that pathways important to regulation against cold pass from the PO/AH region to descend to a point dorsolateral to the mammillary bodies. Severing neural connections of the PO/AH region with single medial or horizontal cuts, or bilateral parasagittal cuts, did not reduce the resistance to overheating. Only the cuts which interrupted most or all connections with PO/AH tissue caused a marked disturbance in regulation against heat. From these findings it appears that the PO/AH pathways subserving heat loss are diffusely distributed and redundant, as pathways subserving other vegetative hypothalamic functions are believed to be. For example, Wolf (47) has obtained evidence for redundant pathways associated with the hypothalamus which subserves sodium intake. In his experiments destruction of the lateral hypothalamus abolished sodium appetite, but lesions which destroyed single hypothalamofugal pathways did not. The idea of redundancy of heat-regulating pathways fits with the general concept that, in the organization of the central thermoregulatory mechanisms, defenses against overheating are better represented than are defenses against chilling. One of the most recent substantive pieces of evidence for this idea is that the brain cells that are sensitive to warmth are also much more numerous than those sensitive to cold (17).
The results obtained on animals with posterior medial cuts indicate that the pathways necessary for thermoregulation do not occupy a paramedial and ventral position in the caudal hypothalamus or in the medial tegmentum of the rat. From these results we conclude that the pathways must occupy a more lateral or dorsal position. This conclusion is in agreement with previous findings of experiments by Sherwood et al. (43) who found that medially placed electrolytic lesions at points near the midline between the optic chiasm and the mammillary bodies did not affect temperature maintenance of rats placed in the cold. As stated earlier, these authors found that resistance to chilling was disturbed by lesions placed at points extending from just above the optic chiasm dorsally, laterally, and posteriorly to a position dorsal to the mammillary bodies and below the thalamus. McCrum (34) also reported that pathways for all temperature regulation lie in the lateral and posterior hypothalamic regions in the rat. His further suggestion that the pathways approach the midline in the upper midbrain is, however, in disagreement with the present result. In cats, Clark, Magoun, and Ranson (13) found that medially placed lesions which did not invade the lateral hypothalumus also did not cause much disturbance in temperature regulation no matter whether they were situated at the level of the infundibulum or the level of the mammillary bodies. The data of Barbour (2, 3) on Rhesus macaques with transections in the posterior hypothalamus and the tegmentum which involved lateral and medial connections also support the importance of lateral temperature-regulation pathways. In the present experiments the lack of significant decreases in body temperature in the 5°C environment after medial cuts near the posterior border of the optic chiasm, near the mammillary bodies, and at points between is consonant with the findings of Chowcrs, Conforti, and Feldman (12) on cold-exposed rats with hypothalamic disconnections. From the present and previous result it seems that the thermoregulatory pathways in the diencephalon and upper midbrain occupy lateral, or at least extraparamedial, positions.

The temperature of the medulla oblongata has been shown to influence both physiological and behavioral thermoregulatory processes (13). The specific region of the medulla oblongata that is known to be thermosensitive is also responsive to injections of prostaglandin E1 (32), a substance believed to be involved in the development of fever. Destruction in this region in the present experiments caused disturbances in resistance to heat in some rats and to cold in others. How can this finding be explained? One possibility is that the lesions destroyed closely spaced thermosensitive cells which are particularly important to thermoregulation in extreme environmental temperatures. The difference in thermoregulatory failures among animals might then be due to differences in the specific populations of temperature receptors destroyed. In this case the rises in body temperature in the heat would be the result of failure of the remaining population of heat receptors in the medulla to act as a second defense and to oppose further elevations in temperature. Selective destruction of cold receptors in the medulla would be responsible for the relatively low resting body temperatures and for low T′s in the cold. To accept this explanation it is necessary to rule out the possibility that the lesions destroyed pathways to thermoeffectors and thus specifically altered heat production or heat loss capacity. The pathways required for regulation against heat and cold (23) and for shivering (7, 8, 45) are believed to be laterally placed at the level of the pons and medulla and thus were not involved in the lesions of the present experiments.

While the results provide further evidence for the importance to thermoregulation of the thermosensitive region of the medulla oblongata, they do not specifically indicate which pathways associated with the region are important to temperature control. As suggested earlier (31), it may be that the medullary thermoreceptors have considerable autonomy in controlling thermoregulatory responses by modifying the activity of cardiovascular and respiratory control mechanisms located in this part of the brain and thus serve as a second line of defense or broadband temperature control. In support of this idea, recent studies by Chai and Lin (11) indicate that medullary temperature receptors alter respiratory rate and cardiovascular responses even after the brain substance above the inferior colliculi in rabbits is removed. Although the exact connections of the thermosensitive neurons which are responsible for these effects have not yet been described, it seems that associations with local respiratory and cardiovascular control mechanisms would be both necessary and sufficient.

The question of a role for medullary thermosensitivity in normal fine temperature control has not been studied. The low T′s in rats with medullary lesions in the present experiment do, however, suggest that the integrity of the thermosensitive region of the medulla is required for temperature control in a neutral thermal environment. If communication between the temperature-sensitive region of the medulla and more rostral structures such as the PO/AH region or the posterior hypothalamus (18) is necessary to the fine control of body temperature, it may be reasonable to expect that the lateral thermoregulatory pathways which pass through the brainstem are responsible for this function.

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