Hypothalamus, temperature regulation, and feeding in the rat

C. L. HAMILTON AND P. J. CIACCIA
Departments of Physiology and Psychiatry, University of Pennsylvania, and Veterans Administration Hospital,
Philadelphia, Pennsylvania 19104

1971.—Rats were implanted with electrodes across the preoptic anterior hypothalamic region (POAH) of the brain. Radio frequency heating of this area elevated its temperature by 1.25°C and resulted in a drop in core temperature and a rise in tail temperature. Twenty-four-hour POAH heating in other electrode-implanted rats resulted in an increase in food consumption in six of eight rats tested. Heating of the ventromedial and posterior hypothalamic resulted in no changes in body temperature or food intake. In no case was water intake increased during the course of POAH heating.

THE HYPOTHALAMUS HAS BEEN PROPOSED AS AN AREA OF THE BRAIN INTIMATELY INVOLVED IN THE REGULATION OF ENERGY BALANCE. An important part of this regulatory system is the maintenance of an appropriate body temperature and Brobeck (3) has suggested that food intake is controlled in appreciation of temperature regulation. This is not to say that feeding does not come under the influence of other control systems, such as cerebral intracellular glucose utilization, when the animal's priority is not temperature regulation.

The work of Spector et al. (13) and Hamilton and Brobeck (10, 11) has demonstrated the close coupling between the preoptic anterior hypothalamic (POAH), temperature regulation, and feeding in the rat. The present work investigated the specificity of the POAH with respect to temperature regulation and feeding in the rat using the techniques of artificial brain heating.

EXPERIMENT 1

Methods. All of the brain heating reported in these studies was accomplished with radio-frequency (rf) current using the output of a Grass model LM-3 lesion maker. The first experiment reports calibration data collected with the Grass instrument. The subjects were seven male Sprague-Dawley rats weighing between 257 and 352 g (mean 309 g) at the time of implantation of the heating electrodes. The electrodes were 0.5 mm in diameter and were made of stainless steel insulated to within 1 mm of the tip with insulating varnish. The tips were cut on a bias so that the larger surface of the electrodes faced toward the midline. Two electrodes were assembled 2 mm apart in a plastic carrier cemented to the skull. The carrier was positioned stereotaxically so that the electrodes were placed equidistant from the midline of the rat, as determined by the superior sagittal suture, at an anterior-posterior location 7.4 mm anterior to the ear bars and at a depth of 8 mm from the top of the skull. All the surgery in this work was performed under Nembutal anesthesia (50 mg/kg). All coordinates are with reference to the DeGroot atlas (6). This area of the brain is referred to as the POAH and is shown along with a set of electrode tracks in Fig. 1.

No temperature-sensing devices were implanted in the brain of the chronic preparations. In all cases where core and tail temperatures were measured, the animals were restrained in a jacket and harness as described by Spector et al. (13). Core temperature was measured by inserting a Yellow Springs thermometer thermometer 5 cm beyond the anal orifice. Tail temperatures were measured by a banjo probe thermometer taped to the base of the tail. Both temperature measurements were monitored with a Grass model 7 polygraph. Except where noted, ambient temperature was 25°C. In all instances, animals were not brain heated within the first 10 postoperative days.

Changes in brain temperature on heating were correlated with the Grass LM-3 settings using one anesthetized rat placed in the stereotaxic apparatus with the electrodes positioned in the POAH. A 26-gauge thermistor probe needle was placed midway between the electrodes.

Results. Figure 2 shows the near linearity between changes in POAH temperature and the Grass LM-3 intensity settings in a test on the anesthetized rat. Although the core temperature of the animal under anesthesia was approximately 3°C below that of an unanesthetized rat, we believe these data to be close approximations to brain temperature changes to be found in the heated implanted animals.

Figure 3 shows the mean drop in core and rise in tail temperatures in the seven chronic implant rats as a function of Grass LM-3 settings. Both functions are linear and the variability of the change in tail temperature is approximately 3 times that of the core temperature. All points on these figures represent maximum changes occurring during the heating session.

The time course of changes in core temperature are shown in Fig. 4 and although at intensities of 25 and 30, at
the end of 60 min, the temperatures appear to continue to fall. We have found that continued heating beyond 60 min did not result in a further drop in temperature.

These data revealed that the use of the Grass LM-3 produced predictable changes in the temperature of the brain, core, and periphery of the rat and enabled us to use the technique for further work on brain heating.

EXPERIMENT 2

Methods. In this study we investigated the interaction between brain heating and ambient temperature. Four animals with a body weight range of 310–352 g (mean 331 g) from experiment 1 were used. Three animals from that experiment had loosened electrodes and could not be included.

The test was conducted in a Hotpack constant-temperature room with ambient temperature controlled within ±0.5 C. Relative humidity was not directly controlled and ranged from 35% at 5 C to 50% at ambient 25 C. Except for the test sessions, the animals were maintained in the regular laboratory space at 25 C ambient and on test days were placed in the constant-temperature room 30 min before activation of brain heating. At least seven days elapsed between tests. A Grass LM-3 intensity of 30 was used for a period of 1 hr of brain heating.

Results. Figure 5 shows that at lower ambient temperatures core temperature was driven to lower levels, albeit a limit appears at 15 C. We did not conduct 2-hr tests under these conditions and it is possible that a longer heating period would have differentiated between 15 and 5 C.

Figure 5 also presents data on changes in tail temperature during one of these brain-heating tests. The effect of ambient temperature alone on tail temperature is shown by the points on the ordinate at 0 time which was in effect 30 min after exposure to the test temperature. It was obvious that during heating at the low temperatures, vasodilation was only slightly noticeable at 15 C ambient and absent at 5 C.
These findings in the rat are similar to the findings on dogs of Fusco et al. (7) who showed that the response of the dog to central heating at ambient 26 C was a 30–40% reduction in rate of heat production and a slight vasodilation. In a cool (14 C) environment, heat production was reduced by only 10% and no vasodilation occurred upon brain heating. In our rats, the large drop in core temperature when the brain was heated at 15 C ambient probably was the result of reduction of heat production although we have no data on this variable. However, in these 1-hr heating tests, our rats were inactive and most of the time were lying on the floor of the cage at all ambient temperatures. Thus, in the cold, the brain-heated rat exhibits a drop in core temperature and no peripheral vasodilation. The question of why certain cold-adjustment mechanisms and not others can be reversed by brain heating remains to be answered.

At 25 C ambient, tail temperature rises then falls during brain heating (Fig. 5). The peak response occurs at 15 min with a return to preheat levels after 60 min. Several interpretations may be made of these data. First, when the POAH is heated at ambient 25 C, core temperature falls and presumably the temperature of the blood prefusing the tail. This in itself could effect a drop in tail temperature and appears to be the most parsimonious explanation. Second, perhaps at ambient 25 C vasodilation mechanisms are labile and cannot be driven for sustained periods. For example, at ambient 30 C we may have been able to get a sustained dilation but this was not tested. Third, with the drop in core temperature following brain heating, the core temperature stabilizes at a lower level and control mechanisms (vasoconstriction) may be activated to prevent further body cooling. This analysis leads to the premise that during brain heating the core temperature is regulated at a new set point.

In addition to the tail temperature response, the brain-heated rat also salivates for approximately 10 min and then stops. Apparently this response, like the tail temperature, cannot be driven for long periods.

EXPERIMENT 3

Methods. This experiment investigated the effects of artificial brain heating of the ventromedial (VM) and posterior areas of the hypothalamus on body temperature. The VM subjects were five male Sprague-Dawley rats weighing between 334 and 344 g (mean 338 g) at the time of electrode implantation. Heating electrodes were implanted as described in experiment 1 except that the anterior-posterior coordinate was 5.4 mm anterior to the ear bars. The posterior subjects were three male Sprague-Dawley rats weighing between 371 and 393 g (mean 379 g) at the time of operation. Heating electrodes were implanted as in the other experiments except that the anterior-posterior coordinate was 2.2 mm anterior to the ear bars and the tips of the electrodes were placed 10 mm below the surface of the skull. All brain heating was accomplished using an intensity of 30 on the Grass LM-3. Core and tail temperatures were obtained in the same manner as in the experiments on the POAH.

Results. Figure 6 shows the location of the electrodes in the VM-heated animals. All five animals showed a slight, but not significant, drop in core and a rise in tail temperature upon heating the VM. We interpret these minimal effects as a result of some heating of the caudal portion of the anterior hypothalamus.

Figure 7 shows the electrode placements in the posterior hypothalamus. Heating here produced no effects on core or tail temperature.

In reference to brain heating and body temperature regulation: 1) artificial heating of the POAH of the rat results in a fall in core temperature and a rise in tail temperature at ambient temperatures above 15 C. Below ambient 15 C, POAH heating is followed by a fall in core temperature but no change in tail temperature. 2) Artificial heating of other parts of the hypothalamus does not result in any significant changes in either core or tail temperature.
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FIG. 6. Coronal section through rat hypothalamus showing electrode tracks terminating in ventromedial area. Tips of electrodes are outlined in black ink. DeGroot coordinate = anterior 5.4 mm from ear bars. OT = optic tract.

In reference to brain heating and food intake: previous work by Spector et al. (13) has shown that thermodal heating of the POAH is accompanied by an increase in food intake in the rat. The present work investigated the effect of VM and posterior hypothalamic heating on feeding. In addition, the effects of 24-hr POAH heating were studied with respect to food and water intake and spontaneous activity.

EXPERIMENT 4A

Methods. This experiment studied the effects of VM and posterior hypothalamic heating on food intake. The subjects were the same animals used in experiment 3. The animals were placed on a 2 hr/day feeding schedule and supplied a mixture of 50% Purina laboratory chow and 50% tap water. After stable base lines for food intake were established, brain heating was initiated, first during the initial hour of feeding only and then only during the 2nd hr. The Grass LM-3 intensity of 30 was used in all cases.

Results. Figures 8 and 9 show no significant differences in food intake during either of the brain heating sessions in either group of animals.

We conclude from the work of Spector et al. (13) and the present studies, that elevation of hypothalamic temperatures does not in any case suppress food intake during 2-hr feeding session. However, heating the POAH increases food intake during a 2-hr feeding session (13) and the next experiment tested the effect of chronic brain heating on feeding.

EXPERIMENT 4B

Methods. This study investigated the effects of 24-hr brain heating of the POAH on the variables of feeding, drinking, and activity.

For these studies an activity wheel (Wahman Co.) was modified by replacing the living portion of the cage with a unit 32 cm wide x 42 cm long x 37 cm high. The wheel was 35.5 cm in diameter and was reversed on its spindle so that the rat could move in and out of the wheel with the heating leads attached to its head (Fig. 10). In addition to the running wheel, there was available to the rat a 2 x 10 cm lever, requiring approximately 10 g pressure to activate an attached microswitch which in turn delivered a 45-mg Noyes pellet at each lever press. The lever was positioned 7.5 cm from the floor of the cage and next to the food delivery cup. Water was supplied ad libitum with a conventional water bottle and stainless steel drinking tube. The rat was connected to the Grass LM-3 through a coiled cable from the head to a swivel connector at the top and middle of the living cage. The entire apparatus was kept in a sound-deadened chamber.

All rats in these studies were male Sprague-Dawley

FIG. 7. Coronal section of rat brain showing electrode tracks terminating in the posterior hypothalamus. Tips of electrodes are outlined in black ink. DeGroot coordinate = anterior 2.2 mm from ear bars. PC = posterior commissure.
weighing between 450 and 525 g at the time of testing. Heating electrodes were implanted as in the previous studies in the POAH area. Correct placements were checked by heating the brain and recording a drop in core and a rise in tail temperature. Animals not showing these physiological changes were discarded.

In all cases, during the 24 hr before the chronic heating tests, the animals were connected to the Grass LM-3 but not heated. Merely attaching the cable to the rat’s head did not affect any of the recorded variables. Light in the apparatus was on from 0600 to 1800 hr.

Results. The data from these experiments are equivocal and, as a consequence, must be considered of a preliminary nature.

Figure 11 shows food data and electrode placement of rat 8D98 heated at a Grass intensity of 25 for 24 hr on 3 different days. For this animal food intake was increased over control levels on each heating day. However, activity levels were not affected and water intake was only slightly reduced.

Table 1 presents data on seven other preparations and indicates that the most consistent response to POAH heating was an increase in food intake. The inconsistencies between animals indicates that the electrode placement within the POAH may be a critical factor. Also of importance may be the parameter of stimulus intensity. We do not have sufficient data on either of these parameters to draw definite conclusions.

Our data on brain heating and water intake in the rat are contrary to those reported by Andersson (2) for goats. Andersson observed significant polydipsia in goats with artificial heating of the POAH. Neither our data nor those of Spector et al. (13) reveal any evidence of polydipsia and, in fact, there is a tendency for all our rat subjects to reduce water intake when brain heated. Presently it is an open question whether increased body temperature or environmental temperature act directly as stimuli for drinking. Hainsworth et al. (8) present convincing evidence for the rat that increased drinking in hot environments follows dehydration resulting from saliva spreading and is not a direct effect of elevated temperature. Budgel (4) presents evidence on rats to the contrary but he did not measure dehydration directly. The following study tested specifically the hypothesis that heating the POAH of the rat is accompanied by polydipsia.

EXPERIMENT 5

Methods. Five male Sprague-Dawley rats, weighing 330–393 g (mean 378) at the time of testing were implanted with heating electrodes placed in the POAH in a manner similar to the previous studies. All animals, on POAH heating at a Grass LM-3 intensity of 30, showed a significant drop in core and a rise in tail temperature. Following this test, the animals were placed on a 23-hr water-deprivation schedule and allowed free access to water for 1 hr/day while in the harness-and-test apparatus described in experiment 1. Food was available at all times in the home cage but not in the test apparatus. After stabilization of the 1-hr water-intake data, the animals were heated during one of the drinking sessions for the entire 1-hr period. Each animal served as its own control.

Results. Figure 12 shows the results of the experiment along with the data for the control days before and after the brain heating. All animals showed a drop in core temperature on the day of brain heating. Four of the animals
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FIG. 11. A: mean cumulative record of food intake of brain-heated rat. On days of brain heating, mean water/food ratios dropped from 0.42 (control) to 0.39. B: photomicrograph of coronal section of brain of rat 8D98 showing electrode tracks terminating astride the POAH. Tips of electrodes are outlined in black ink. DeGroot co-ordinate = 7.4 mm anterior from ear bars. AC = anterior commissure, OC = optic chiasm.

drank less than their control intake on brain heating while the fifth rat showed no change. The large variability on the day of heating obscured the mean differences and the Student's t test was not significant. Figure 13 portrays the data for one of these rats. During the brain heating session, core temperature fell, skin temperature rose, and water intake was suppressed. There is no evidence of damage to the temperature-sensitive areas of the POAH.

The true significance of these data is the fact that none of the animals increased water intake when brain heated even though they were water deprived. All of our evidence on the rat strongly suggests that heating of the POAH does not result in an increase in water intake.

DISCUSSION

Recent experiments by Corbit on the rat (5) and Adair et al. (1) on the squirrel monkey indicate that behavioral

TABLE 1. Summary of results of 24-hr brain heating in seven rats

<table>
<thead>
<tr>
<th>Rat</th>
<th>Food (Pellets</th>
<th>Activity (Rev)</th>
<th>Water ml</th>
<th>Grass Int</th>
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<td></td>
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<td>Con</td>
<td>Heat</td>
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<td>985</td>
<td>310</td>
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</table>

FIG. 12. Water intake during 1-hr sessions (means ± se). Body temperature at end of each session is recorded within bars (means ± se). Heat = day of brain heating. Con = nonheating days before and after heating.

FIG. 13. Changes in water intake, core and tail temperatures in brain-heated rat. Photomicrograph of brain of this rat is shown in Fig. 1.
thermoregulatory behavior (bar press for heat or cold) is closely proportional to the sum of the displacements of hypothalamic and skin temperatures from their neutral points. From his data, Corbit estimates that skin temperature is given approximately 2 times the weight of hypothalamic temperature in the integrated control of thermoregulatory behavior. The influence of skin temperature may also be the explanation of our present physiological finding in experiment 1 which showed that peripheral vasodilation was blocked during brain heating in a cold environment.

The study of body temperature regulation has evolved over the past decade into a fruitful blending of physiological control and regulation and behavioral science. The interaction of food intake and temperature regulation constitutes a portion of that problem area and its history was recently reviewed (9) but presently, in the light of new data, needs to be brought up to date.

In 1963, Andersson (2) reported that heating the POAH of the goat suppressed feeding in the fasted animal. Conversely, he reported that POAH cooling increased feeding in sated animals. Since that time, Spector et al. (13) have shown the opposite effects of POAH heating and cooling in the rat. Assuming no differences between rats and goats in regard to the neurophysiological organization of the temperature and feeding systems, we must account for the differences in the behavioral data. Close inspection of the procedures of Andersson reveals that his heating and cooling techniques altered brain temperature beyond physiological limits. The heat stimulus was at least 48°C, warm enough to coagulate protein and cause tissue damage. In the cooling experiments, increased food intake was not noted until the anterior portion of the ventromedial hypothalamus was cooled. The increased feeding may have resulted from the effects of a functional ablation of the ventromedial area. For purposes of argument we believe the sum of the evidence so far indicates that heating the POAH is followed by increased feeding and cooling the POAH results in decreased feeding. If one considers feeding as being part of the control system of temperature regulation, and further, that feeding is, in essence, behavioral thermoregulation, then certain dilemmas arise when comparing feeding with other behavioral thermoregulatory behavior.

In general, when the POAH is heated the initial physiological responses of the rat are similar to those seen when the rat is environmentally warm stressed. POAH cooling results in physiological responses seen when the rat is cold stressed. Bar pressing for external heat or cold follows POAH cooling and heating respectively. Depending on the altered POAH temperature, the rat acts as if it were warm or cold “outside” (5, 12). The data on food intake are contrary to these data and we must explore whether our position taken in the 1967 paper needs revision. That position stated: “Generally and simply put, all the data lead us to believe that in the homeotherm, when conditions exist that call forth heat retention mechanisms, feeding is enhanced. When heat loss is appropriate to circumstances, feeding is depressed.” (9, p. 316)

Let us examine first the thermoregulatory behavior of rats bar pressing for heat in a cold environment. Weiss and Laties (14) have studied closely that behavior. Their work showed that a fall in skin temperature preceded bar pressing before there was any change in core temperature. These authors showed that rats in the cold bar pressed for heat in a manner that resulted in a fairly constant skin temperature. Corbit has also stressed the importance of skin temperature in the control of thermoregulatory behavior. He states, “The greater emphasis apparently given to $T_s$ (skin temperature) in the control of behavioral thermoregulatory responses is appropriate to the anticipatory function of thermoregulatory behavior” (5, p. 258). Whether the behavior is anticipatory is open to debate since, in the cold, skin temperature changes very rapidly and precedes the bar pressing behavior. Nonetheless, the temperature of the periphery appears to be important to the elicitation of thermoregulatory behavior. It would appear that skin temperature, being more labile than core temperature, has been incorporated into the feedback system controlling not only core temperature but skin temperature itself. Thus, the first line of defense after cold or heat stress, is alteration in the status of the heat exchange regulators. Whether the behavior is anticipatory is open to debate since, in the cold, skin temperature changes very rapidly and precedes the bar pressing behavior. Nonetheless, the temperature of the periphery appears to be important to the elicitation of thermoregulatory behavior.

Consideration of feeding as thermoregulatory must take into account these peripheral events. Considering the case for POAH heating and increased food intake, we postulate the following events. On the initiation of brain heating, food intake should be suppressed. As Fig. 5 shows, initially, under such conditions at ambient temperature 25°C, there is peripheral vasodilation as inferred from the rise in tail temperature, and a drop in core temperature. Later, tail temperature falls and the core temperature stabilizes. During this period of heat retention, food intake is initiated and enhanced in defense of the core temperature. The rat under such conditions is in a chronic state of relative heat retention. We have made some preliminary observation on the minute-to-minute records of feeding and changes in tail and core temperature in the rat during POAH heating. On initiation of brain heating, feeding was suppressed and later enhanced when tail temperature began to fall. Presently, we do not have enough data to be more than speculative about these conditions. Since Spector et al. (13) did not record tail temperature, we have little information on the possible interactions between POAH cooling and the suppression of feeding that they observed.

Feeding is believed to be controlled by a complex of factors and there are other variables that we have not investigated that may be affected by brain heating. We have no data on the effects of POAH heating on gut motility or utilization of glucose by hypothalamic tissue, to name but two factors. Until we learn more, there is the possibility that brain heating affects food intake indirectly through other mechanisms controlling feeding.

In summary of brain heating and food intake: in the rat, there is evidence that artificial heating of the hypothalamus does not result in alterations of feeding behavior. There is strong evidence that heating the POAH results in an increase in food intake in both short term (2 hr) and long term (24 hr) food intake. Presently we conclude that the interactions of temperature regulation and feeding cannot
be predicted from any one measure of body temperature, but will be understood only when all the conditions of thermoregulation are considered. To the extent, and under the conditions when temperature regulation and feeding interact, the most fruitful hypothesis appears to point to relative changes in skin temperature as being predominant in the control of food intake. Presently there is no need to revise our 1967 (9) position.

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REFERENCES


