Control of thermoregulatory behavior by brief displacements of hypothalamic temperature¹

ELEANOR R. ADAIR, John B. Pierce Foundation and Yale University, New Haven, Conn. 06519

When local hypothalamic temperature is changed, squirrel monkeys behaviorally change their environmental temperature in the opposite direction by a proportional amount. Skin and deep body temperatures shift in the same direction the environment does. Several pairs of offered air temperatures, which the monkeys must alternate to select their environment, yield similar functional relations between the behavioral response and hypothalamic temperature.

Reports of behavioral thermoregulation in many species indicate that the strength of a thermoregulatory response is directly related to the environmental temperature, and consequently to the skin temperature. Typically, the animal Ss are placed in a constant environment, ranging from -10° to $+50^{\circ}\text{C}$, and are allowed to barpress for timed reinforcements of radiant or convective heating, or convective cooling, whichever is appropriate. Experiments using rats (Satinoff, 1964; Murgatroyd & Hardy, 1970; Corbit, 1970), pigs (Baldwin & Ingram, 1967), baboons (Gale, Mathews, & Young, 1970), and squirrel monkeys (Adair, Casby, & Stolwijk, in press) have further indicated that behavioral thermoregulation may be related to the temperature of the medial preoptic area of the hypothalamus. This area in the brain stem is presumed to be an integrating center for physiological thermoregulatory responses, and temperature-sensitive neurons have been found here in many species (Hardy, Hellon, & Sutherland, 1964; Nakayama, Hammel, Hardy, & Eisenman, 1963).

The experiments described below, an extension of work already reported (Adair et al, in press), provide additional evidence that the behavioral response is linearly related to the displacement of the hypothalamic temperature from its neutral level, when the displacement is relatively brief (10 min). Specifically, the experiments demonstrate that the environmental temperature chosen by the animal is relatively independent of the external stimulus conditions and depends primarily upon his hypothalamic temperature.

METHOD

Four adult male squirrel monkeys,

Saimiri sciureus, served as Ss. Thermode and thermocouple re-entrant tubes were implanted unilaterally in the medial preoptic area of the hypothalamus. The stereotaxic coordinates for the thermode (a sealed stainless steel tube with an o.d. of .039 in.) were: A 12.5, L 0.5, D +1.0 (Emmers & Akert, 1963). The placements were verified by biplane X-rays and histologically. Temperature-controlled water was forced through the thermode at the rate of 7 ml/min to shift the preoptic temperature within the range 35° – 43°C . The preoptic temperature was measured by a copper-constantan thermocouple inserted in a re-entrant tube (a sealed 21-ga stainless steel tube) centered 2.0 mm lateral to the thermode.

Hypothalamic, rectal, ambient, and three skin temperatures were monitored during behavioral temperature regulation. During the experiments, the monkey was restrained inside a small styrofoam compartment that was heated and cooled by convection. A valve system allowed air from one of two thermostatically controlled air sources to circulate through the compartment. The monkey learned to pull a chain to operate the valves, thereby selecting between two preset air temperatures. A different pair of air temperatures was used in each experiment. Air temperature pairs studied were: 60° and 20°C , 55° and 15°C , 50° and 10°C , and 45° and 5°C . Under long-term exposure, all air-source temperatures appeared to be noxious to the animals, who typically alternated between the available two so as to achieve an average air temperature of about 35° – 36°C .

The effects of brief displacements of hypothalamic temperature on thermoregulatory behavior were determined in 16 experiments. Every 10 min, the hypothalamic temperature was raised or lowered by a different amount relative to the undisturbed (neutral) hypothalamic temperature. Ambient and body temperatures were monitored once every minute by a computer-controlled data-acquisition system.² The percentage of each minute the monkey spent in the warm or the cool air was calculated from a continuous recording of temperature at the air outlet of the animal's compartment.

RESULTS

Typical results for a single experiment appear in Fig. 1A. Manipulations of the hypothalamic temperature of the monkey produce changes in rectal temperature,

mean skin temperature, and the air temperature he selects. When the hypothalamus is warmed, the monkey lowers the average air temperature in his compartment, and rectal and skin temperatures fall. Conversely, when the hypothalamus is cooled, the monkey raises the average air temperature, and rectal and skin temperatures rise. When the air temperatures available are 10° and 50°C , as in this experiment, the animal chooses the 50°C air for the full 10-min period whenever the hypothalamus is cooled to 37°C or below. The figure also shows that smaller and smaller hypothalamic temperature displacements produce body and air temperature shifts in the appropriate direction, but of smaller and smaller magnitude. A more quantitative presentation of this result appears in Fig. 1B. Here the behavioral measure, the percentage of each 10-min period the animal chose the warm air, is plotted as a function of the average hypothalamic temperature during that period. The relation is approximately linear over the range explored. (This range is necessarily limited because there is a possibility of

Fig. 1. (A) Changes in rectal temperature (T_r), mean skin temperature (T_s), and air temperature (T_a) selected when the hypothalamic temperature (T_H) of one monkey was alternately raised and lowered every 10 min. (B) The percentage of each 10-min period spent in the 50°C air plotted as a function of the hypothalamic temperature during that period.

incurring local tissue damage at hypothalamic temperatures above 43°C and because this particular animal chose the 50°C air 100% of the time at all temperatures below 37°C.) The point at which the function crosses the ordinate at neutral hypothalamic temperature (39.3°C) represents this monkey's preference for 50°C air (when paired with 10°C air) under normal conditions. The slope of the solid line may be related to the experimental conditions, particularly the duration of each hypothalamic temperature displacement and the pair of air temperatures provided. Nevertheless, it seems that, to a first approximation, the control exerted over behavior is a linear function of hypothalamic temperature when that temperature is subjected to brief displacements around its neutral value.

Figure 2 shows representative results for the four pairs of air source temperature studied. The behavioral measure plotted in each panel is the percentage of each 10-min period spent in the warmer of the two air temperatures offered. All of the functions show a linear relation between thermoregulatory behavior and hypothalamic temperature very similar to Fig. 1B. In addition, the slopes of the functions are very nearly the same for all the pairs of air temperatures.

A measure of the preferred average air temperature for any specific hypothalamic temperature can be derived from the behavior under the assumption that the time-averaged air temperature is linearly related to the percentage of time spent in the warm vs the cool air. Thus it can be shown that, when hypothalamic temperature is neutral, these monkeys all choose an average air temperature of 35°-36°C no matter what pair of air temperatures is available. For example, a 32% choice of 60°C air is equivalent to an 81% choice of 45°C air in that both yield an air temperature close to 35°C. (These percentages are accurate only when the cold air is 40°C lower than the warm air with which it is paired.) Since the slopes of the four functions in Fig. 2 are nearly the same, it is evident that the monkeys behave appropriately to achieve a specific average air temperature for each level of hypothalamic temperature. Air temperatures calculated in this manner are in close agreement with those measured during the course of the experiments.

As the warmer of the two air source temperatures is set closer to the preferred neutral of 35°C, the monkeys have more difficulty obtaining the additional heat they need to oppose hypothalamic cooling. Thus, the animal in Fig. 2D chooses the

45°C air 100% of the time whenever his hypothalamic temperature is displaced to 39°C or below, but he must desire more exogenous heat than he can obtain under these stimulus conditions. In this situation, we might expect to see a greater dependence upon physiological mechanisms of heat production (such as increased metabolic rate, vasoconstriction, and perhaps shivering) since behavior fails to yield the heat gain signaled for by the hypothalamus.

DISCUSSION

The results of the 16 experiments indicated that the behavioral response is linearly related to hypothalamic temperature when that temperature is briefly displaced around its neutral value. Apparently, in these experiments the external stimulus conditions are easily sensed by the animal because they are accurately adjusted so as to provide an environmental temperature that is directly related to hypothalamic temperature. In other words, hypothalamic temperature per se is the principal stimulus to the behavior that controls the environment and thereby adjusts the skin and other body temperatures.

The linear relations shown in Figs. 1 and 2 imply that in this kind of experiment the behavioral response (R) is stimulated by the linear sum

$$R = a\Delta T_{hy} + b\Delta T_s$$

where ΔT_{hy} is the displacement of the hypothalamic temperature from its neutral level; ΔT_s is the change in mean skin and other body temperatures called for by the animal; and a and b are rate constants that depend upon the experimental conditions. This kind of linear system, in which the response is proportional to both skin and hypothalamic temperatures, has recently been proposed for the behavioral response by Corbit (1969), and has proved very useful in the past for the description of physiological thermoregulatory responses (Stolwijk & Hardy, 1966; Smith & James, 1964).

In the formulation above, although ΔT_{hy} can be specified, ΔT_s cannot because too little is yet known about the distribution and magnitude of the temperature shifts within the body that result from heating and cooling the skin. However, such a general mathematical

Fig. 2. The percentage of each 10-min period spent in the warm air plotted as a function of the hypothalamic temperature during that period. Air source temperatures available were (A) 60° and 20°C; (B) 55° and 15°C; (C) 50° and 10°C; and (D) 45° and 5°C.

formulation is useful because it provides an organizational framework for consideration of the variables affecting the behavior. In the present case, for example, the equation implies that there is no change in the slope of the function as ΔT_{hy} changes from positive to negative values. This implication is borne out by the experimental results and suggests that hypothalamic sensitivity is equal for both heating and cooling. Whether the same equation will also describe the behavioral responses produced by prolonged displacements of hypothalamic temperature has not been determined in the present experiments, but there is no reason to expect that it should. Experiments where hypothalamic temperature was displaced for periods up to 2 h indicated that the initial behavioral adjustments of air temperature, so dramatically displayed in the present experiments, tend to be modified over time (Adair et al, in press). The behavior pattern shifts as the total heat content of the animal gradually shifts. This should be expected, after all. Although the monkey in Fig. 1 sometimes chose the 50°C air for an entire 10-min period, it is evident that he could not make this choice indefinitely, for this would soon produce severe hyperthermia and death. Therefore, the type of behavioral change depicted in Figs. 1 and 2 represents only a transient phenomenon. It is nonetheless very potent and describes, at least to a first approximation, the control exerted over behavior by neural signals from the hypothalamus.

REFERENCES

- ADAIR, E. R., CASBY, J. U., & STOLWIJK, J. A. J. Behavioral temperature regulation in the squirrel monkey: Changes induced by shifts in hypothalamic temperature. *Journal of Comparative & Physiological Psychology*, in press.
- BALDWIN, B. A., & INGRAM, D. L. The effect of heating and cooling the hypothalamus on behavioral thermoregulation in the pig. *Journal of Physiology*, 1967, 191, 375-392.
- CARLISLE, H. J. Heat intake and hypothalamic temperature during behavioral temperature regulation. *Journal of Comparative & Physiological Psychology*, 1966, 61, 388-397.
- CORBIT, J. D. Behavioral regulation of hypothalamic temperature. *Science*, 1969, 166, 256-257.
- CORBIT, J. D. Behavioral regulation of body temperature. In J. D. Hardy (Ed.), *Physiological and behavioral temperature regulation*. Springfield, Ill: Chas. C Thomas, 1970, in press.
- EMMERS, R., & AKERT, K. A *stereotaxic atlas of the brain of the squirrel monkey* (Saimiri Sciureus). Madison: University of Wisconsin Press, 1963.
- GALE, C. C., MATHEWS, M., & YOUNG, J. Behavioral thermoregulatory responses to hypothalamic cooling and warming in baboons. *Physiology & Behavior*, 1970, 5, 1-6.
- HARDY, J. D., HELLON, R. F., & SUTHERLAND, K. Temperature sensitive

- neurons in the dog's hypothalamus. *Journal of Physiology*, London, 1964, 175, 242-253.
- MURGATROYD, D., & HARDY, J. D. Central and peripheral temperatures in behavioral thermoregulation of the rat. In J. D. Hardy (Ed.), *Physiological and behavioral temperature regulation*. Springfield, Ill: Chas. C Thomas, 1970, in press.
- NAKAYAMA, T., HAMMEL, H. T., HARDY, J. D., & EISENMAN, J. S. Thermal stimulation of electrical activity of single units in the preoptic region. *American Journal of Physiology*, 1963, 204, 1122-1126.
- SATINOFF, E. Behavioral thermoregulation in response to local cooling of the rat brain. *American Journal of Physiology*, 1964, 206, 1389-1394.
- SMITH, P. E., & JAMES, E. W. II. Human

- responses to heat stress. *Archives of Environmental Health*, 1964, 9, 332-342.
- STOLWIJK, J. A. J., & HARDY, J. D. Temperature regulation in man—A theoretical study. *Pflügers Archiv*, 1966, 291, 129-162.

NOTES

1. This research was supported by USPHS Grant ES00354-02. The technical assistance of Miss Ruth Harildstad is gratefully acknowledged. A portion of the results was presented to the Psychonomic Society, St. Louis, 1969. Address reprint requests to Eleanor R. Adair, John B. Pierce Foundation, 290 Congress Avenue, New Haven, Conn. 06519.
2. The data acquisition system was designed and instrumented by Mr. James U. Casby of the John B. Pierce Foundation Laboratory.

The relationship of acid-soluble nitrogen in rat brain to avoidance behavior

MARTIN GOLD, MARK MILLER, HENRY ALTSCHULER,
MORTON H. KLEBAN, and M. POWELL LAWTON
Gerontological Research Institute
Philadelphia Geriatric Center, Philadelphia, Pa. 19141

A limited avoidance training schedule was used to train albino Wistar rats. The rats were sacrificed immediately after training. Rats with no training were used as a control group. Acid-soluble nitrogen was measured in three brain sections (cerebrum, brain stem, and cerebellum). Each brain section exhibited an increase in acid-soluble nitrogen with training, suggesting that the increase was due to an enlargement of the amino acid pool.

In two previous reports from our laboratory (Gold et al, 1969, 1970) nonprotein nitrogen (NPN) was estimated by subtracting the contribution of protein nitrogen, by assuming the nitrogen content to be 16%. The first report (Gold et al, 1969) showed that the calculated NPN value was significantly depressed 2 h after escape training, but not immediately after termination of the training. Since the protein concentration rose as the NPN plummeted, it was speculated that this drop could reflect utilization of amino acids for protein synthesis. A second report (Gold et al, 1970) studied the relationships among the cerebellum, brain stem, and cerebrum with respect to control, avoidance, and avoidance-plus-extinction behavior for total nitrogen and estimated NPN. Significant differences in NPN were found for the brain sections, and aged animals had higher concentrations of NPN than the young in the avoidance-plus-extinction training condition. Those values were significantly correlated with extinction behavior in the aged but not in the young rats.

This report represents studies that were carried out to ascertain if the results noted

for the calculated NPN would still be obtained with direct chemical analysis of acid-soluble nitrogen. Trichloroacetic acid was used to precipitate the protein and nucleic acid in three brain sections (cerebrum, brain stem, cerebellum) and the acid-soluble nitrogen determined. A control group and an avoidance-trained group were analyzed.

METHOD

The experimental apparatus was a 30-in.-long automated straight runway maze. By rotation of the endboxes, acting alternately as start- and goalboxes, around a stationary stem, animals could receive aversive training without handling between trials. It was a massed training procedure, the time between any two trials being 16 sec. The Es will supply a detailed description of the apparatus and methodology upon request.

Twenty-four albino Wistar rats were used. Twelve were assigned to a control group that received no training. Twelve rats received limited avoidance training that consisted of 20 trials. On each trial, the animal was given a 1.0-mA electric shock, but the S could, by running, avoid most of the punishment. Immediately upon