Thermodes and Theories*

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Many investigators seeking the nature of temperature regulation in homeotherms (endotherms) have heated or cooled the whole or parts of the body by a great variety of ingenious methods. Their work ranges from the pioneer work of Ackermann (1867), who injected cold blood into the jugular vein of a dog, to the very modern work of Bligh (1957, 1966), who has been studying the effects of heated or cooled inspired air in sheep and calves kept at different ambient temperatures. In this brief review, only the methods used for specifically heating or cooling localized areas in the brain will be considered. Five different techniques for this purpose have been employed, excluding simple electrical stimulation which has multiple and, therefore, ambiguous effects.

These techniques include: (1) changing the temperature of the blood supply to the head or changing the volume of blood flow in the head; (2) perfusion of the ventricles of the brain with warm or cold saline solutions (Hammouda, 1933); (3) heating or cooling by circulating fluids or gases (including condensing refrigerant gases) through tubes planted acutely or chronically in specific intracranial areas; (4) heating an area between two electrodes through which radio frequency (RF) alternating current is passed; and (5) heating or cooling by conduction through metal probes attached to heat sources or sinks on the exterior of the head, e.g., via Peltier biothermodes (Stuart, Ott and Cheshire, 1962; Hayward et al., 1965) or water coils (Folkow, Ström and Uvnäs, 1949a.)

As a preface to this discussion of local heating and cooling methods, we might consider the work of Kahn (1904) who, by looping a tube around the carotid arteries of the rabbit and passing water of varying temperatures through the tube, was able to heat the blood supply to the entire brain and observe the consequent thermoregulating responses. Since that time, many have used "carotid loops" for the same purpose; Moorhouse (1911), Thauer (1939, 1964) and others have externalized and bathed the carotid arteries as well as the jugular veins, thus controlling the temperature to and from the head.

Sixty years after Kahn's experiment, Downey, Mottram and Pickering (1964) used a similar cuff on the internal carotid of the rabbit in order to cool the blood a fraction of a degree, and they observed increases in O_2 consumption.

McCook, Peiss and Randall (1962) and Hayward (1967) have demonstrated that, simply by occluding the arterial blood supply, the brain temperature is raised. Similarly, if cerebral blood flow is augmented, as in the case of blood pressure increases induced by high P_{CO_2} (Hayward, 1967), the brain temperature falls. McCook et al. also demonstrated that hypothalamic temperature was lowered further than aortic temperature by barbiturate. This lowering of brain temperature was attributed to increased blood flow to the hypothalamus.

Circulating Liquid Thermodes

Barbour (1912) was probably the first investigator to heat and cool a specific area in one part of the brain. Following the suggestion of H. Meyer, he placed "thin metal double tubules" (Fig. 1) in the brains of rabbits, the tips "meeting the frontal end of the corpus striatum," and passed hot and cold water through these thermodes. These were acute experiments under ether anesthesia, yet they yielded clear-cut results. Barbour was able to show rectal temperature responses opposite in direction to that of induced brain temperature changes, as well as to observe mechanisms of heat loss and conservation, such as peripheral (ear) vasoconstriction and vasodilation. He reported that 42 C was the lowest temperature of the probe that would produce hypothermia, and 33 C the highest that could produce fever. Of course, it is now evident from later work that his limits
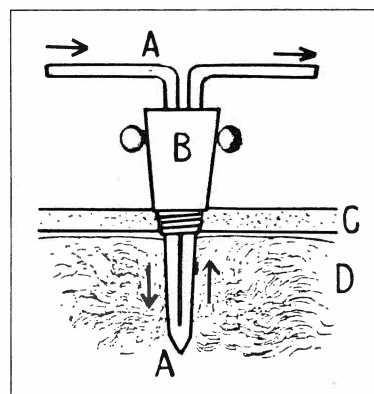

Fig. 1—The first thermode used for heating or cooling specific loci in the brain. A—probe tubule; B—cylinder with studs; C—skull; D—brain. (Reprinted with permission from *Arch. Exp. Pathol. Pharmakol.* 70: 1, 1912.)

could have been considerably narrower had his thermodes been closer to the preoptic area. Bazett, Alpers and Erb (1933) showed that a cat with the corpora striata, cortex and thalamus removed could still regulate body temperature; this followed an earlier demonstration in the same species by Keller and Hare (1932a, b) that, without the hypothalamus, there was no temperature stasis.

A very perceptive observation by Barbour (1912) and, later, by others, that is frequently overlooked by reviewers was that the extent of rectal temperature (RT) change produced by the thermode was limited by the ambient temperature; thus, during cold weather, Barbour was able to produce increases of RT of 2.65 C, but in June and July, he could only produce a maximum increase of 1.1 C with the same cold probe. Using similar thermodes, Prince and Hahn (1918) confirmed Barbour's work, utilizing conscious animals (cats).

Since Barbour's pioneering experiments, the circulating liquid thermode technique has gone through many modifications and has been found to have a wide variety of usages. For example, Byck and Dirlick (1963) have developed a four-pronged thermode assembly through which a refrigerant fluid can be passed, thus producing a "wall of cold" which can serve to anesthetize neural tissue in the plane of the fork. By this means, one may produce reversible *cerveau isolé* or *encéphale isolé*. Cryogenic surgical ablation techniques employing liquid nitrogen or other freezing agents, which represent further extensions of the liquid thermode method, will not be reviewed here.

Adams (1964) has described a prefabricated assembly for chronic implants in cats consisting of two liquid-perfused thermodes with nearby thermistors. These thermodes have been maintained in healthy animals for as long as two years. As with Barbour's thermode, the one designed by Adams is not insulated along the shank and will heat or cool tissues dorsal to the area of tip placement. Other investigators (e.g., Satinoff, 1964) have added insulation, such as polyethylene, around the shank of U-shaped needles, but the degree of heat exchange through the insulation *in situ* is not known. Using a technique described by Lilly (1958), some (e.g., Fusco, 1959; Fusco, Hammel and Hardy, 1959) have implanted chronic reentry tubes into which both a thermode and a temperature measuring element can be inserted for the experimental period only, and then removed.

Ström (1950c) has employed rectangular silver tanks attached to the dura, ventral to the hypothalamic areas of cats, to study the effects of heating and cooling upon polypnea, thermal panting, and peripheral vasoconstriction. He found more pronounced effects from heating than from cooling, but his diagram shows thermode location beneath the lateral hypothalamus as well as more rostral and medial placements. As previous workers had discovered, the temperature of the periphery was a limiting factor upon the effects of central thermal stimulation. Andersson and Larsson (1961) employed tubes ending in a wedge-shaped silver tank in goats' brains, while Baldwin and Ingram (1966) have used stainless steel tubes ending in a copper tank—the assembly coated with plastic—in the rostral hypothalamus of pigs. Under these conditions the respiratory rate of the pig increased at a high ambient temperature to over 200/min., whereas cooling the hypothalamus brought the rate down to 20/min. However, the pig did not press a bar for external heat at high ambient temperatures even when the hypothalamus was cooled.

Gangs of thermodes straddling the hypothalamus in a single animal have been used to study more precisely the loci and magnitude of specific effects (Hammel, Fusco and Hardy, 1959; Hammel, Hardy and Fusco, 1960; Hammel et al., 1963). By means of circulating water, the hypothalamic temperature was "clamped" at fixed levels in dogs and monkeys. Ear and rectal temperatures, shivering, and panting were monitored while ambient temperature was shifted. In a cool environment, brain heating inhibited shivering. Shivering was also elicited in a neutral environment at the termination of brain heating, after core temperature had dropped. As a result of these experiments, Hammel and his colleagues proposed a "proportional control" of body heat, with a variable set point. Observations of hypothalamic temperature shifts in the monkey—of 1.5 C downward during sleep and upward with waking—convinced them that the control system was not a simple one. In describing their work, they stated, "The objective for this study was to obtain a quantitative relationship between hypothalamic and skin temperature and the thermoregulatory responses of the animal. The objective was based on the assumption that there is a unique thermoregulatory response for each combination of skin and hypothalamic temperatures in the resting animal. The observations, however, did not support this assumption." This succinct statement might well be applied to all other attempts, to date, to write a simple two-factor control equation.

Recently another thermode employing circulating fluids has been designed by Spector (unpublished data) to heat or cool smaller areas of tissue than was hitherto possible. This thermode, which can also be used for electrical recording from, or stimulation of, the locus that is heated or cooled, has been employed both for studies of intracranial electrical self-stimulation (Spector and Hamilton, 1967) and for feeding behavior studies (Spector, Brobeck and Hamilton, 1968)

under the influences of brain heating and cooling and of changes in ambient temperature.

Radio Frequency (RF) Heating

Before the turn of the century, d'Arsonval (1898) demonstrated the thermogenic effect of RF currents in living tissues of man and rabbit. It was Cloetta and Waser (1914), however, who applied this technique to the study of temperature regulation by applying heat to the head from external electrodes. Another 24 years elapsed before Magoun, Harrison, Brobeck and Ranson (1938) performed their classic experiment in which many areas were straddled by RF electrodes in an attempt to map out the relative heat sensitivities, in terms of physiological responses, of specific loci in the brain. Extensive searching with RF probes through many areas of the forebrain and midbrain of the cat revealed only a limited area which, when heated, elicited occasional foot-pad sweating and "polypneic panting" (the authors did not state whether or not there is any kind of panting *without* polypnea). The most sensitive areas found began at "the ventrocaudal part of the telencephalon, between the anterior commissure dorsally and the optic chiasma ventrally" and extended "a little further forward than the preoptic area and the crossing of the anterior commissure." A less reactive area extended caudally and dorsally through the medial portions of the hypothalamus and ended in the central gray of the mesencephalon. Rectal temperature changes were not pronounced beyond the depression resulting from anesthesia, but these experiments demonstrated that heat loss mechanisms could be activated even at subnormal core temperatures.

Hemingway et al. (1940) used a single oval-shaped gold foil electrode implanted on the ventral surface of the hypothalamus near the optic chiasma of a dog, together with a large indifferent electrode on the surface of the shaved head. They reported that centrally applied heat led to termination of shivering at low ambient temperatures and an elevation of ear surface temperature as great as 8 C, but they were unable to elicit panting. They suggested that, since they could not replicate the panting seen by Magoun et al. (1938), the heat loss center was higher up, perhaps in the thalamus. In retrospect it seems that Hemingway and his co-workers did not apply the heat as closely to the preoptic area as did Magoun et al., and this may account for the failure to elicit panting. Folkow, Ström and Uvnäs (1949a, b) using pairs of probes similar to those of Magoun et al., applied RF heating to the "anterior hypothalamus" of cats and dogs. They also reported cutaneous vasodilation after two minutes of brain heating (Δ brain T $= \sim 5.5$ C) and absence of panting. They found that, while blood flow to the skin increased, there was no change in muscle blood flow, and blood pressure did not drop. Because peripheral vasodilation persisted undiminished during long periods of central heat, they concluded that it is not a thermal gradient but an absolute temperature in the brain that provides the adequate stimulus for the temperature regulating response. Their results contrast with the finding of C. L. Hamilton (unpublished data) that the tail temperature of the rat rises for about 10 to 20 minutes and then slowly falls during continued RF heating of the preoptic area. One important demonstration reported in the paper of Folkow et al. (1949a) showed that the responses to the RF probe could not be attributed to electrical stimulation; the same response was also elicited with silver probes heated with hot water by conduction from the outside of the skull. In a follow-up series (Folkow et al., 1949b; Folkow, 1955) it was shown that the loss of peripheral vasoconstrictor tone induced by central heating could not be demonstrated in sympathectomized cats or dogs, although the constriction could still be evoked by adrenaline and abolished by acetylcholine or heating of the sciatic nerve. Experiments with cross-circulated, eviscerated cats demonstrated that the primary vasodilation was not hormonally mediated. Thus, the pathway from the hypothalamus was established as being neural, sympathetic, and not mediated via motor segments of the dorsal roots.

Clark (1950) showed that the principle effects of RF radiation on tissues are due to the heat generated. This was substantiated and further quantified by Murphy, Paul and Hines (1950), Herrick and Krusen (1953) and Davis and Mayer (1954). Radio frequency heat may be employed to make discrete tissue lesions and has found application in human neurosurgery (e.g., Aronow, 1960), although its use has been supplanted in part by cryogenic techniques. Davis and Mayer further showed that whereas RF heating in a cold environment did not produce vasodilation, it did induce polypnea along with a *decrease* in O_2 consumption. Such apparently "contradictory simultaneous" effects of so-called contradictory stimuli to the brain and to the periphery were also seen by Hardy and his colleagues (Hardy, 1961). They were able to elicit simultaneous panting and shivering in a dog by heating the hypothalamus until core temperature had dropped. Upon cessation of heating, the dog shivered; with the resumption of brain heating, the animal both shivered and panted.

In a series of papers, Ström (1950a, b, c, d) reported on heating and cooling of the "heat loss center" in cats, dogs, and rabbits. In these papers, the relative influences of central versus ambient temperatures were tested, using peripheral vasoconstriction and polypnea as the indices of response. He found that, in cats, maximum vasodilation could be elicited by

central heating at 39.5 C to 40 C, but that (contrary to Magoun et al.) panting required a higher temperature. In anesthetized cats, he observed no response to cooling the same area. When the skin was cooled to 30 C, vasodilation in response to brain heating was not observed. He concluded from these and other results that thermoreceptors outside the hypothalamus were involved importantly in shivering and panting responses. He further showed that the peripheral responses could be elicited in decorticated animals.

Using RF electrodes in unanesthetized dogs, other investigators (Fusco, Hammel and Hardy, 1959; Fusco, Hardy and Hammel, 1961) also attempted to assess the relative influences of central versus peripheral factors. They found that the shivering induced by a cool environment could be inhibited by brain heating; that shivering could be produced in a warm environment upon the cessation of brain heating, after core temperature had dropped.

Von Euler and Söderberg (1957) studied the effects of RF heat upon gamma motor activity, electroencephalogram (EEG) and shivering in cats and rabbits; they concluded that "hypothalamic thermoreceptors project upon the activating relay system of the brainstem." They found that moderate heat inhibited gamma motor activity and shivering synchronized the EEG, whereas excessive heat desynchronized the EEG. Anesthesia of various types abolished the EEG effects. Of course, it was well known not only that anesthesia may alter the results of any physiological study, but also that varying levels of heat may produce quite different effects; this study, however, pointed to specific electrophysiological changes.

Von Euler (1964) reported on the most carefully quantitative experiments with RF heat to date. Sixteen RF electrodes were implanted about the preoptic and supraoptic regions of the rabbit, and

heat stimuli were applied in very small increments. Hypothalamic temperature was increased 0.2, 0.3, and 0.5 C while skin and rectal temperatures and respiratory rates were recorded and analyzed. Because a stimulus in the brain consisting of $\Delta T = 0.3$ C could produce a drop in rectal temperature of 3.0 C, von Euler called this an "open loop" gain (response/stimulus ratio) of 10. He also concluded ". . . in conditions where the internal temperature is higher than the set point the temperature regulation is governed chiefly by the thermodetectors. . . . Cutaneous temperature receptors as well as the thermoceptive structures in other hypothetical locations outside the pre- and supraoptic regions are apparently not able to prevent the considerable fall in body temperature that is elicited by the slightest temperature increase in the anterior hypothalamus." These latter conclusions do not seem to be fully justified by the experimental evidence presented. Barbour (1912) demonstrated that, in the *rabbit,* low ambient temperature attenuated the hyperthermic response to a cold brain probe. Ström (1950b) showed that in the *cat,* ambient temperature affected core temperature responses to thermal stimulation of the brain. Spector et al. (1968) showed that, in the *rat,* high (35 C) ambient temperature reduced the degree of hypothermia elicited by a hot preoptic probe.

Von Euler's work raises another very important problem which is not mentioned in his 1964 paper. It is not clear why an artificially induced hypothalamic temperature change of 0.3 C should induce a drop of 3.0 C in rectal temperature, whereas normal fluctuations in hypothalamic temperature do not have any negative directing effect upon core temperature (Hamilton, 1963; Abrams and Hammel, 1964, 1965; Bligh, 1966; Delgado and Hanai, 1966) unless it is assumed that the "set point" fluctuates with every random fluctuation in brain

temperature. In this case the argument becomes circular, and the term set point begins to lose its meaning.

Many models have been proposed (e.g., Bligh, 1966; Stolwijk and Hardy, 1966) to explain the "set" of the set point, but, as the model makers concede, none of these fits all the experimental data.

Temperature-Sensitive Areas in the Brain

In recent years, beginning with the work of Nakayama, Eisenman and Hardy (1961), a number of investigators (e.g., Hardy, Hellon and Sutherland, 1964; Murakami et al., 1966; Nakayama, 1966; Cabanac and Hardy, 1967; Eisenman and Jackson, 1967; Wit and Wang, 1967) have studied the firing rate of a single neuron subjected to thermal stimuli in various loci of the brain. Units have been found in the preoptic area which respond to a 10 C increase of temperature by increasing their firing rates as much as 18 times the resting rate ($Q_{10} = 18$). Some units respond only in one portion of the temperature scale, other units in another portion. Still others have been found with Q_{10} as low as one and some with negative Q_{10}. Eisenman and Jackson (1967) have found some of these unusually heat-sensitive neurons more dorsally, in the septal area, but they thought these probably were second-order units. In a recent study of units in the "preoptic-anterior hypothalamus" region of cats, Wit and Wang (1967) found some units that responded with increased firing frequency to increases in ambient temperature before brain temperature was elevated, and others that responded only to brain temperature changes. Cabanac and Hardy (1967) reported temperature-sensitive units in the thalami of rabbits. It has been suggested by Hardy (1961) and his co-workers that these specialized cells in and near the preoptic area might be

units in a comparator-type thermostatic system.

Heat can serve as a stimulus to other areas of the brain, particularly the respiratory centers (e.g., Holmes, Newman and Wolstencroft, 1960; Hardy, 1961). Indeed, nerve cells, endings and fibers, as well as systems in homeotherms, are, as might be expected in any biochemical system, responsive to changes in temperature (e.g., Ström, 1950d; Zotterman, 1959; Thompson, 1964; Gillary, 1966; Hofmann, Parsons and Feigen, 1966). The particular significance of the work reviewed here is that the responses of many mammals to heating or cooling a specific area of the brain are those peculiar to the mechanisms of thermal homeostasis.

One of the results of the thermode work of the past 57 years has been to localize the brain areas that are most responsive to heat and that are most closely associated with body heat-regulating mechanisms. These appear to be the rostral hypothalamic-preoptic and -supraoptic regions in all mammals studied.

Recent work on leucocytic pyrogens by Cooper, Cranston and Honour (1966), showing that these pyrogens act upon the same "centers," but probably not elsewhere, adds further evidence of the unique nature of these areas. Additional anatomical and physiological evidence has been extensively reviewed (Bligh, 1966; Cooper, 1966; Cranston, 1966).

The quantitative influence of the temperature regulating "center" or "centers," as opposed to the influence of thermal receptors elsewhere in the body, remains to be determined. There still are many conflicting data on the exact necessary and sufficient conditions for shivering, polypnea, sweating, vasoconstriction and vasodilation, hormone release, and other indices of reaction to heat or cold stresses.

The identification (nature and location) of the temperature regulating and behavior regulating centers in the central nervous system appears to have been, and still is, a long process of zeroing in on the target, although there are some investigators today, for example, Bligh (1966) and Morgane (1961), who feel that this is a futile endeavor, due to the diversity of the control systems as well as their interconnections with others. Morgane has gone so far as to call the search for centers a new kind of "phrenology"; but this sophisticated point of view does little credit to the majority of the pioneering and fruitful investigations that have yielded most of our concrete knowledge in this field.

There are at least two more dissenting voices on the importance of the rostral hypothalamic complex as an essential center for temperature regulation. Thauer (1935, 1939) and Blair and Keller (1946) have offered evidence, from sectioning and ablation studies, that mammals can survive and retain at least partial temperature regulation without the hypothalamus. Bligh (1966) has attempted to reconcile the bodies of conflicting evidence by proposing a dual temperature regulatory system in homeotherms consisting of a coarse control, which protects the animal against extreme fluctuations in body temperature and is derived from pre-mammalian groups, and a fine control, which is phylogenetically more recent. The anatomical loci of the controls for these two systems are presumed to be quite separate—the first in the rostral hypothalamus, the second in the periphery.

Summary and Epilogue

This brief outline reviews some of the important studies done with various types of thermodes employed for heating or cooling loci in the brain and discusses some sources of the findings relevant to our understanding of temperature regulation in mammals.

It becomes evident that physiological theories cannot be interpreted without an intimate knowledge of the techniques used in accumulating the evidence. The same data have sometimes been evaluated differently, leading to diametric theories (see discussion of the Andersson et al. papers in Spector, Brobeck and Hamilton, 1968). There are many other problems that have been only hinted at here. How "physiological" is an animal with one or more telephone poles (electrodes, thermodes, etc.) jammed through his brain? How representative are thermal gradients measured in non-living gels, in anesthetized animals, in animals with metallic conductors to the exterior of the cranium? What physical, chemical and biological mechanisms can account for neurons with Q_{10} of 18? Yet the search continues, and the tools are still being refined. In the period between the writing of this paper and its publication, enough additional publications have appeared to warrant an appendix as long as the original text. However, the basic problems are still the same and it is my hope that the above will be useful as an introduction to this field.

This review neither covers all of the work of the authors cited nor cites all the investigators who have used similar techniques, but attempts to give a representative sampling of past work in this area.

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