Intracerebral temperatures in free-moving cats

JOSE M. R. DELGADO AND TAIJI HANAI
Department of Physiology, Yale University School of Medicine, New Haven, Connecticut

The existence of cerebral mechanisms responsible for the regulation of body temperature has attracted the interest of investigators since the last century (32, 35), and attention has been centered on the hypothalamus (4) because of the disturbances in thermoregulation that followed lesions of the hypothalamus or of neighboring areas (5, 6; see also 21), because of the possibility of changing body temperature by hypothalamic heating and cooling (13, 14, 18, 19, 23), and due also to the existence of temperature-sensitive neurons in the preoptic region (29). It was therefore natural that the majority of the investigators considered the hypothalamus as an important indicator of intracerebral temperature, and studied this structure in rats, cats, dogs, oxen, and monkeys during sleep, wakefulness, spontaneous activity, and other experimental situations (1-3, 12, 13, 18, 20, 31, 34, 38).

The pioneer work of Serota and Gerard (37) and Serota (36) revealed a temperature gradient in the brain with the cortex being 1.4 C cooler than basal regions. Anesthesia lowered brain temperature whereas sensory stimulation caused a rise localized in the receptor areas of the brain. Changes in cerebral temperature were related to the extra heat produced by the active neurons plus the local vasodilatation induced by its metabolic products. During sleep, there was a drop in brain temperature that was greater in the hypothalamus than in cortical areas and, in general, Ammon's horn and the tail of the caudate nucleus showed smaller fluctuations than the hypothalamus.

In spite of the differences in intracerebral temperatures mentioned by Serota and Gerard (37), many authors have assumed more or less explicitly that the brain is thermally uniform. Ogata (31) found that the thermal responses of the thalamus were similar to those of the anterior lobe of the brain. Kawamura and Sawyer (26) reported that during the transition from sleep to arousal, the changes in temperature were similar in the preoptic region and in the posterior hypothalamus, neopallium, and pons, with delays of 10 sec in other cerebral areas with respect to the preoptic region. Rampone and Shirasu (33) implanted thermistors in rats at the coronal suture, 7 mm below the cortex, assuming that the temperature of this point reflected "uniform changes throughout the entire cranium, including the hypothalamus." In a study about "cerebral temperature changes accompanying sexual activity in the male rat," Hull et al. (23) also considered the temperature of cerebral cortex, where the thermistor was implanted, as representative of the whole brain.
MATERIALS AND METHODS

The experiments were performed on 10 cats with thermal sensors in locations indicated in Table 1. Several constantan-copper thermocouples 0.43 mm in diameter were stereotaxically implanted within the brain of each cat under anesthesia with a technique similar to that for implantation of electrodes described elsewhere (7, 8). The leads were permanently fixed to the skull with dental cement and the skin was carefully closed around the implantation block. In addition, one more thermocouple was introduced into the left carotid artery, passed under the skin of the neck, and attached to the block on the head. In some experiments, other thermocouples were attached to the ear or introduced into the rectum for short periods of time. The wires were insulated with Teflon and the thermocouple tips were exposed for electrical recording or stimulation of the brain. To avoid possible artifacts, there were no connections or joints in the constantan-copper wires between the implanted tips and the recording instrument. In the initial experiments, recordings were made of the thermal emf, with a reference couple in a thermally insulated ice-water bath, but as it was convenient to know both the absolute and the differential temperature of each cerebral structure, we used the system shown at the right of Fig. 4. Using two different amplifiers, it was possible to record simultaneously the temperature of one cerebral thermocouple against the reference in ice water and against another cerebral thermocouple.

Two or three days after implantation, the experiments began with continuous recording of intracerebral temperatures for periods of a few hours to a maximum of 3 days, using a Grass polygraph model P7. When desired, the intracerebral electrical activity was recorded from pairs of thermocouple tips on the same polygraph or was taped on a four-channel Precision Instrument recorder. Electrical stimulations through the thermocouples were delivered by a Grass S-4 instrument with an isolation unit, and voltage and milliamperage were monitored on a two-channel oscilloscope.

The connecting leads permitted the cat mobility within a special cage measuring 2 x 2 x 2 ft that was electrically shielded and thermally insulated. Behavioral observations were made visually through the front of the cage or were recorded by 16-mm black and white time-lapse photography (9) taking one picture every minute (see Fig. 4). The cage had diffused, low-level illumination from 8:00 AM to 8:00 PM, and no light was available during the night. The environmental temperature was 25 ± 1 C. Food and water were given ad lib., and the animals seemed to enjoy a comfortable existence. After completion of the experiments the cats were anesthetized and perfused with saline and with 10% formalin. The brains were cut stereotaxically in 10-mm blocks to prepare frozen sections for histological analysis and localization of the recording tips (see Table 1 and Fig. 1).
intracerebral temperatures

Fig. I. Frozen section of the brain of cat 3 showing one tract ending in the posterior hypothalamus and another in the hippocampus.

Carotid artery was opened to check that it had been patent during the experiments.

Controls

Before implantation, the thermocouples were tested by immersing them in bundles of four in a circulating water bath at 40 °C which cooled off to 35 °C in about 30 min and was warmed again to 40 °C; this cycle was repeated three or more times. The thermocouples used had a uniform response better than 0.02 °C.

Results

Spontaneous Variations of Temperature

In all cats studied, intracerebral temperature displayed variations during a 24-hr period as high as 1 °C, some of which were related to behavioral factors or to ingestion of food. A typical continuous record of temperature taken simultaneously from the skin, blood, cortex, and hypothalamus in cat 6 appears in Fig. 2. The thermal changes had a similar trend in the four recordings, diminishing in the evening and again early in the morning. The ear pinna temperature was the lowest and most variable. The cerebral cortex was cooler than the hypothalamus, and the temperature of the intracarotid blood was similar to that of the hypothalamus, dropping below the hypothalamic level at several points in the record. This fact was important because it demonstrated that some areas of the brain could be warmer than the circulating blood, and therefore the source of heat should be related, not to a passive transfer, but to active local metabolic processes. A closer analysis of the temperatures revealed that the graphs were similar but not identical and, for example, at the first datum line of Fig. 2, the curve has a sharp rise in the ear, a moderate rise in the cortex, and a drop in hypothalamus and carotid, demonstrating that the rapid variations were not a passive reflection of blood temperature. Other portions of the curves in Fig. 2 also revealed discrepancies in the sign or the shape of the thermal changes. In the rest of the cats, intracerebral temperatures presented similar oscillations with some lags and reversals among different cerebral structures, as shown for example in Fig. 3, where the lower three curves expressed the differential temperature between the thalamus and the posterior cruciate gyrus, pyriform cortex, and carotid blood as calculated from the recorded values. In this experiment, the thalamus was warmer than the other two cerebral areas but cooler than the blood, except for three periods (2:00, 5:00, and 8:00 AM) when thalamic temperature...
rose above that of the intracarotid blood. This figure clearly showed the lack of thermal uniformity. For example, at 1:00 AM, the differential thalamus-pyriform and thalamus-carotid temperatures rose, whereas thalamus-crusicate gyrus decreased slightly. At 2:30 AM, a peak in thalamus-carotid temperature was not reflected in the brain, and after 3:00 AM, while this curve decreased, both intracerebral differentials rose. These differential values were calculated from the graphs, and to study thermal correlations among different areas of the brain with greater accuracy, further experiments were performed in which the local temperature was recorded against another reference point in the brain, as shown in Fig. 4. In this way, the local temperature and the magnitude of thermal difference between selected cerebral areas were measured simultaneously. The differences in thermal reactions of different areas of the brain are documented in Fig. 4 and were also observed in the experiments of sensory and electrical stimulation described later.

Spontaneous fluctuations in temperature appeared in all recordings and were classified as fast fluctuations when a change of 0.2 C or more developed during a period of 30 min or less, and as slow fluctuations when a change of more than 0.2 C occurred within a period of 4 hr or longer. Fast fluctuations usually developed in a few minutes and the most rapid recorded change was 0.4 C within 5 min. However, the shifts could be even greater during drinking of ice water or during electrical stimulations, as explained later. Figure 3 shows the values for maximum and minimum temperature in cat 7 during each 30-min period, and for each of the recorded points. The distance between the two maximum and minimum lines indicates the amplitude of fast fluctuations, whereas the whole graph shows the contour of the slower fluctuations. The vertical dashed lines of the graph represent the number of temperature changes exceeding 0.2 C within each 30-min period, irrespective of the sign, and revealed that the region of greatest variability was the amygdala, while the intraarterial temperature remained more constant with very few fast fluctuations. Table 2 is a summary of fast thermal fluctuations in five cerebral areas, carotid blood, and rectum, showing the relative stability of intraarterial blood and rectum, and the thermal lability of the brain, with the greatest amount of fluctuations present in the pyriform region.

Behavior and Intracerebral Temperature

By direct observation, the temperature of the brain and also of the blood seemed to be related to the general activity of the animal, decreasing during periods of rest, and increasing while the cat moved around. To analyze this correlation with objectivity and accuracy during long periods of time, the recordings of intracerebral temperature were synchronized with electroencephalo-
Awakening of cat, as recorded by time-lapse photography and EEG, was accompanied by a thermal rise mainly affecting the pyriform cortex. Diagram at right shows method for simultaneous graphic tracings and with time-lapse photography of the behavior of the animals. In addition, a miniature mercury switch was attached to the head of the cat in order to record continuously on the polygraph small movements of the animal during periods of rest that would not be detected by photography.

In the awake animal, changes from rest to motor activity produced minor rises in the intracarotid temperature, whereas the intracerebral temperature increased if the thermal level preceding the behavioral activity was relatively low, around 38-38.5 C, and was not modified if the initial thermal level of the brain was high, above 38.5 C. In one typical case of thermal increase recorded photographically, cat 10 lay down for about 15 min, resting with eyes open and small postural changes, after which it spontaneously got up and explored the cage, walking around for about 3 min; then it lay down looking around with its head erect, and finally extended its hind limbs, turned to one side, rested its head on the floor and closed its eyes. As soon as the cat was on its feet, the cerebral temperature began to rise, reaching a peak in 3 min with the following magnitude of increase in each region compared with thermal values of the resting state: posterior cruciate gyrus: 38.35-38.55 (+0.20), pyriform cortex: 38.40-38.62 (+0.22), preoptic region of hypothalamus: 38.65-38.75 (+0.10). In 20 different experiments when the cat spontaneously initiated motor activities, the highest recorded temperature increases were 0.53 C for motor cortex, 0.63 C for pyriform cortex and 0.3 C for hypothalamus.

In general, movements such as standing up, walking, eating, playing, and fur licking increased the intracerebral temperature if the cat had been resting and the temperature was relatively low, but not if the initial thermal level was high, indicating that there was no specific thermal reaction in the brain during any of these activities, and that the increase depended more on the initial thermal level than on motor performance. Some other types of behavior were accompanied by specific thermal changes, and are described below.

Sensory Stimulation

To analyze the possible effects of sensory stimulation on brain temperatures, the following experiments were performed:

a) While a cat was resting, the investigator hissed and made threatening gestures for about 1 min, inducing an alerting response in the animal during which its EEG decreased in amplitude and increased in frequency. Pyriform cortex temperature increased approximately 0.2 C in 75 sec and then slowly decreased. Smaller changes
were recorded in other cerebral areas and all together the effect appeared related to the alerting of the animal.

b) Tape-recorded sounds of a friendly cat, angry cat, barking dog, and excited monkey were each presented for about 1 min, resulting in a temperature rise of 0.1–0.2 °C in the pyriform cortex and thalamus, but these changes also seemed dependent on the general alerting effects of the sounds rather than on specific emotional reactions, because the effect of different stimuli was similar.

c) When a live mouse was introduced into the cat's cage, the cat attacked it in less than 30 sec, and after the mouse was quickly withdrawn by the investigator, the cat continued meowing and looking for it for several minutes. Recordings showed that the pyriform cortex temperature started rising immediately after the mouse was introduced and before the cat initiated an attack. Thalamic temperature (ventralis medialis) started rising with a 50-sec delay and only after the aggressive performance. Both pyriform and thalamic temperatures continued rising while the cat searched for the mouse and they reached a peak change of 0.3 °C in about 8 min.

d) Cat Mina, with electrodes in the amygdaloid region, was introduced into the cage of cat 10, which had intracerebral thermocouples. Following electrical stimulation, Mina hissed, growled, spit, and attacked cat 10, which flattened its ears, lowered its head, withdrew, and tried to escape. This defensive reaction in the attacked animal was accompanied by an increase in intracerebral temperature which was similar to the changes observed during spontaneous hostility, as explained below. After several stimulation experiments, as soon as Mina was introduced into the cage with cat 10, there were offensive-defense displays with growling and hissing, and cat 10 cowered in a corner. Recordings showed that its pyriform cortex temperature increased immediately after the animals confronted each other, and reached a peak change of 0.22 °C in about 1 min, whereas the thermal reaction was smaller in the hypothalamus and posterior cruciate gyrus, where temperatures rose only 0.05 °C and 0.1 °C, respectively.

These four experiments may be interpreted as a demonstration of moderate and general increase in intracerebral temperature by alerting stimuli (a and b) and a greater, faster, and more specific thermal reactivity in the pyriform region evoked by stimuli involving emotional responses of the cat (c and d).

Sleep—Wakefulness

In agreement with the literature, we found a slow decrease in intracerebral temperature when the cat was falling asleep, and a rise when the animal awakened, with the difference that during sleep, brain temperature rose from time to time even in the absence of postural changes, as soon as the cat opened its eyes or moved its ears or head, indicating that motor activity of the body was not essential for thermal variations in the brain. Minor sensory stimulation produced, for example, by a person walking into the room or by a small unusual noise, was accompanied by a noticeable rise in intracerebral temperature, even if there was no opening of the eyes or any other detectable change in behavior. In these cases, the essential factor proved to be the modifications of the electrical activity of the brain from the sleep pattern of high voltage, slow waves to the arousal state of low voltage, fast activity. Noises which did not change the electroencephalographic activities did not modify brain temperature either.

Table 3 is a sample of the quantification of temperature increases recorded in different structures and animals during spontaneous transitions from sleep to wakefulness, as determined by behavioral and electroencephalographic observations. The greatest temperature increases in these experiments were recorded in the pyriform cortex, where the mean change within 1 min was 0.10 °C, and the maximum was 0.5 °C; the smallest change was in the intraarterial carotid blood where there were no detectable thermal variations in 50% of the cases; the mean change was 0.01 °C and the temperature rose only once to 0.10 °C. In only 5% of the spontaneous arousals did the intracerebral temperature remain constant and this was probably due to an insufficient period of sleep.

One example of the thermal effects of waking up is shown in Fig. 4. In this case, the temperature of the pyriform region rose sharply only for the short time the cat was awake, and returned to the base line as soon as the cat fell asleep again. Recordings of temperature in other areas showed that the differential pyriform-hypothala-
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Petting

In all cats tested, petting proved to be one of the most effective stimuli for raising intracerebral temperature, and one example is shown in Fig. 5. When the resting animal was first stroked, it reacted with friendly behavior by rubbing its face and body against the experimenter's hand, and the pyriform temperature rose sharply within seconds. It was significant that the thalamic and posterior cruciate gyrus temperatures responded after a greater delay and with a lesser degree of intensity, and that the intracarotid temperature did not rise, but declined slightly. This fact clearly demonstrated that regional brain temperatures can vary independently of the blood temperature, with some relative autonomy among different cerebral structures, and that the pyriform area was more reactive than the thalamus and motor cortex.

Urination and Defecation

In all cats temperature recordings were continued for many hours during which several spontaneous urinations and defecations occurred. Postural changes such as raising the leg produced a minor or negligible modification of the intracerebral temperature, whereas the abdominal effects of emptying the rectum caused a thermal rise of greater amplitude in the amygdala and pyriform cortex than in the hypothalamus, and barely affected the intracarotid temperature. After eliminatory activities were completed, there was a decrease in intracerebral temperature. It should be emphasized that these changes were not as pronounced as those associated with petting.

Cold Drinks

When cats were offered ice cream, cold milk, or cold water, in all cases there was a considerable decrease in the temperature of carotid blood, rectum, and brain. The magnitude of this effect was related to the temperature of the substance offered, and to the speed and amount of its ingestion, and it therefore depended on how hungry or thirsty the animals were. In general, when a thirsty cat drank 10 ml of water at 10°C in 2 min, there was a decrease of intracarotid temperature which started with a delay of 2–10 sec and reached a peak change of approximately 0.6°C in 2–3 min which lasted for about 10 min, but this effect was variable and in the same animal the intracarotid thermal drops ranged between 0.3 and 1.5°C. There was also a general temperature decrease in the brain after a delay of 10–50 sec that was usually of less amplitude than in the blood, ranging between 0.2 and 0.9°C in different cerebral areas without clear anatomical specificity. One example of this phenomenon is presented in Fig. 6, in which drinking 10 ml of water at 10°C caused an almost immediate and precipitous fall of intracarotid temperature, followed by thermal drops in pyriform cortex and hypothalamus which, as revealed by the differential recording, were faster and greater in the hypothalamus than in the pyriform area. In contrast, drinking of liquids at temperatures between 30 and 45°C did not modify the body or the intracerebral temperature of the animals.

To investigate the changes in body and cerebral temperatures resulting from an increase in the environmental temperature, two animals were tested when the
usually the cats moved and tried to escape and the results were contaminated by motor and emotional reactions. Within normal values. No significant differences in temperature, and that in about 1 hr the temperatures went down to about 37 C in 10 min and then returned to normal in 20 min. The recordings showed that, in general, the temperatures of rectum, amygdala, pyriform cortex, motor cortex, and hypothalamus rose to about 0.5-0.9 C above the control levels, that panting of the animals could not prevent this rise, and that in about 1 hr the temperatures went down within normal values. No significant differences in temperature change were recorded in the cerebral areas explored.

**Local Heating**

In three cats brain temperatures were recorded while a localized area of the animal’s skin was being heated, but usually the cats moved and tried to escape and the results were contaminated by motor and emotional reactions. To avoid this problem, cat 2 was immobilized with 7 mg/kg gallamine (Flaxedil) and then the following experiments were performed:

**Heating the head.** Application for 4 min of a 150-w light, beamed at the top of the head from a distance of 30 cm while the body of the cat was protected from this light, produced a considerable thermal increase in the posterior cruciate cortex that, as indicated in Table 4 (see also Fig. 7A), reached 1.95 C in 5 min, and then took about 0.5 hr to return to normal. The increase of temperature was less marked in the orbital cortex and minor in the rectum, showing that application of heat to the outside of the head affected the temperature of the superficial areas of the brain considerably, in spite of the protection of fur, teguments, bone, and circulation. Figure 7A demonstrates that the posterior cruciate cortex reacted almost immediately, whereas there was a clear delay in the orbital cortex.

**Heating the body.** In this experiment the cat’s head was protected from the 150-w light that was aimed at its exposed body, and, as indicated in Table 4 (see also Fig. 7B), the greatest elevation of temperature was recorded in the rectum; this rose 1.20 C in 0.5 hr, whereas the increase in temperature in the posterior cruciate cortex was slower and less pronounced.

**Heating the carotid artery.** The left side of the carotid artery was exposed under local anesthesia and cleaned for 2 cm. Then the artery was continuously irrigated for 30 sec with Ringer solution at 60 C and, as shown in Table 4, the temperature of the ipsilateral orbital cortex promptly increased, reaching a peak of 0.3 C in 40 sec, whereas there was no thermal change in the posterior cruciate cortex. These results were repeated several times and in some cases rectal temperature was recorded and it was not affected by irrigation of the carotid artery.

**Cooling the carotid artery.** In the same preparation described in the previous paragraph, the exposed carotid artery was irrigated for 30 sec with Ringer solution cooled to 2 C, resulting in a considerable decrease in the temperature of the ipsilateral orbital cortex which ranged in different experiments from 0.3 to 1.0 C, without any detectable effect on the temperatures of the posterior cruciate gyrus or the rectum. The fact that heating or cooling the carotid blood selectively influenced the temperature of the posterior cruciate gyrus and that of the orbital cortex suggested a considerable circulatory independence of these regions.

**Administration of Drugs**

Acetylcholine. Intraperitoneal administration of 7% solution of acetylcholine chloride (Merck) in doses below 1 mg/kg did not produce reliable changes in intracerebral temperature in spite of the appearance of clinical symptoms such as some restlessness and increase in salivary and lacrimal secretions. It was necessary to inject larger amounts that produced retching and vomiting in order to influence the temperature of the brain, and the results are shown in Table 5. In all cases doses of 2.5 mg/kg acetylcholine produced a marked decrease in intracerebral temperature, with ranges from 0.40 to 0.85 C, reaching a peak a few minutes after drug administration and lasting between 1/2 and 3 hr in different animals. In all cases decreases in brain temperature started before the appearance of retching or vomiting, indicating their independence from these autonomic phenomena.

**Adrenaline.** Intraperitoneal injection of 2% l-epinephrine hydrochloride (Glauccon) did not produce any change in brain temperature when the dose was below 10 µg/kg, but higher amounts proved to be effective, as shown in Table 5. In cat 10, after administration of 40 µg/kg adrenaline, the animal started licking, cleaning its fur, drinking water, and moving around for about 4 min and then lay down quietly for the rest of the experiment. The temperature of the pyriform cortex reached a peak change of 0.44 C in 1 min after administration of the drug and this effect was more rapid and pronounced than thermal increases in the hypothalamus.

**TABLE 4. Effect of localized heating (cat 2 curarized)**

<table>
<thead>
<tr>
<th>Head, spotlight for 4 min</th>
<th>Delay, sec</th>
<th>dT in 1/100 C</th>
<th>Time to Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior cruciate gyrus</td>
<td>25</td>
<td>195</td>
<td>5 Min, 35 sec</td>
</tr>
<tr>
<td>Orbital cortex</td>
<td>90</td>
<td>90</td>
<td>6 Min, 20 sec</td>
</tr>
<tr>
<td>Rectum</td>
<td>55</td>
<td>15</td>
<td>6 Min, 30 sec</td>
</tr>
<tr>
<td>Abdomen, spotlight for 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior cruciate gyrus</td>
<td>310</td>
<td>50</td>
<td>10 Min, 30 sec</td>
</tr>
<tr>
<td>Orbital cortex</td>
<td>207</td>
<td>88</td>
<td>14 Min, 30 sec</td>
</tr>
<tr>
<td>Rectum</td>
<td>60</td>
<td>120</td>
<td>9 Min, 30 sec</td>
</tr>
<tr>
<td>Carotid artery, Ringer 60</td>
<td>C for 30 sec</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior cruciate gyrus</td>
<td>10</td>
<td>0</td>
<td>40 Min</td>
</tr>
<tr>
<td>Orbital cortex</td>
<td>5</td>
<td>-50</td>
<td>180 Min</td>
</tr>
</tbody>
</table>

In this and subsequent tables d1 indicates change in recorded temperature between control level and peak of effect.

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and posterior cruciate gyrus. The highest dose of adrenaline tested was 500 μg in cat 3, which produced initial restlessness followed by urination, defecation, and a depressed state with circulatory collapse of the animal 90 min after the injection. The amygdala temperature rose to a peak change of 1.1°C in the short period of 80 sec, whereas the increase in temperature in hypothalamus and other areas of the brain was more moderate, as indicated in Table 5.

Chlorpromazine. Doses below 1 mg/kg did not affect the temperature of the brain, but 2 mg/kg produced a clear thermal decrease in all cerebral areas, as indicated in the experiment shown in Table 5, without being accompanied by clear changes in the spontaneous behavior of the cat, which spent a good part of the day dozing as usual. A larger dose of 6 mg/kg chlorpromazine increased the amount of time that the cat slept, and produced a considerable drop in intracerebral temperature, as indicated in Table 5.

Electrical Stimulation of the Brain

The anatomical structures electrically stimulated in different animals included orbital cortex, posterior cruciate gyrus, amygdala, pyriform cortex, nucleus ventralis medialis of the thalamus, and mesencephalic reticular formation. In all cases, stimulation of the brain with intensities below motor thresholds did not produce detectable changes in cerebral temperatures. In general, threshold excitations which induced discrete motor responses had little or no effect on cerebral temperature and it was necessary to use higher intensities to evoke clear thermal changes. The crucial element seemed to be the induction of electrical seizures whether or not they were accompanied by motor manifestations. A typical example is shown in Fig. 8A, in which electrical stimulation of the reticular formation in cat 4 with intensities of 0.7 ma produced a discrete alerting without noticeable changes in electrical activity or in temperature. Excitation with 0.8 ma produced a small local seizure that increased in amplitude and duration if the electrical stimulation was augmented to 0.9 or to 1.0 ma, and this electrical afterdischarge was accompanied by thermal rises of progressively increasing amplitude. Simultaneous electrical and thermal recordings from the hypothalamus, nucleus ventralis lateralis of the thalamus, and posterior cruciate gyrus demonstrated the existence of a similar and moderate spread of electrical seizure activity to these regions which, however, reacted thermally in a different manner, with the thalamic temperature increasing as much as that of the stimulated reticular area, whereas the hypothalamus showed a more delayed and discrete response and the motor cortex temperature slowly decreased. A thermal correlation between reticular formation and thalamus was also shown in the experiments of thalamic stimulation in which a localized increase in electrical activity was induced, with some spread to other cerebral regions (see Fig. 8B), and at the same time the temperature increased mainly in the stimulated area and in the reticular formation, with little effect in the hypothalamus and no reaction in the posterior cruciate gyrus.

The distribution of the thermal reactions that accompanied the electrical stimulation of the brain proved to be related to the site of stimulation, and as shown in Fig. 9A, excitation of the amygdala produced a clear local increase in temperature, a pronounced effect with considerable rebound in the posterior cruciate gyrus, and more discrete reactions in the thalamus and hypothalamus. Changes in intracerebral temperatures, especially when accompanied by motor activity or by motor convulsions, could either be secondary, reflecting modifications of body temperature, or primary and dependent on metabolic or vasomotor local factors. To investigate these possibilities, stimulations of the amygdala strong enough to produce motor seizures were applied while skin and blood temperatures were being recorded. These experiments demonstrated that the thermal increase in the amygdala coincided with a decrease in the intracarotid blood temperature and therefore was not secondary to possible thermal changes in the body. This effect was reliable, and four typical curves are presented in Fig. 9B. Only in one case, when the increase in the amygdala temperature was of less amplitude and duration than usual, as shown by the solid line of the figure, the blood temperature showed only a slight decrease. In all other cases, the intracarotid temperature went down considerably. Changes in the skin temperature of the ear pinna were less reliable but tended to decrease initially, reflecting vasoconstriction. We may conclude that intra-

![Image](http://ajplegacy.physiology.org/10.1152/ajplegacy.02200.2017)
cerebral thermal rises evoked by electrical stimulation of the brain do not depend on the temperature of the blood and may occur even during thermal drops in the body. Also, we should accept the thermal heterogeneity of different areas of the brain since the amygdala and motor cortex are more reactive than thalamus and hypothalamus during electrical excitation of the amygdaloid nucleus. A summary of the thermal reactions of different cerebral structures during electrical stimulation of motor cortex (posterior cruciate gyrus) and of amygdala is presented in Table 6.

With intensities at threshold level producing a discrete motor response, such as a flexion of the contralateral hindlimb, or closing of the contralateral eye, the thermal increase in the brain including the stimulated areas was between 0.0 and 0.04 C and in only one case the temperature of the stimulated amygdala rose to a peak change of 0.08 C. Results were also similar in other experiments when thalamus and reticular formation were stimulated at threshold levels, as shown in Figs. 8, A and B.

It was difficult to evoke localized seizures in the motor cortex because of their tendency to spread, but in cat 3, by careful adjusting of intensity, it was possible to produce localized motor afterdischarges in the contralateral hindlimb for 5-6 sec that were accompanied by a moderate and rather localized increase of temperature, shown in Table 6. In the amygdala, it was easy to produce typical localized electrical afterdischarges that were accompanied by discrete symptomatology such as facial twitching, staring, and salivation, and there was meowing following the electrical afterdischarge. In these cases,
Thermal increases up to 0.13°C were recorded in the amygdala, and other cerebral areas were also moderately affected, as shown in Table 6. The greatest thermal effects were obtained when electrical stimulations produced generalized seizures. The temperature of the stimulated point often increased as much as 0.3°C in less than 3 min, and thermal increases were recorded from all implanted thermocouples. Table 6 and Figs. 8 and 9 show that the greatest thermal reaction was not always recorded in the stimulated region. For example, in cat 5, excitation of the postcruciate gyrus with 1 mA increased the local temperature only 0.10°C, whereas in the thalamus it rose 0.21°C.

Stimulation of the orbital cortex produced motor and thermal effects similar to those obtained by motor cortex excitation, with the difference that the evoked responses were localized mainly in the contralateral face, and that in this region we obtained the greatest changes in temperature, which in one case increased 1°C during the afterdischarge, and afterward fell 2°C in less than 5 min, remaining below control levels for more than 10 min. In typical cases, stimulation of the orbital cortex with 1–1.5 mA induced afterdischarges starting with twitches in the contralateral eye and face, and continuing with the animal falling to its side and having mild generalized motor convulsions that lasted for 15–25 sec. The pattern of electrical recordings during one of these seizures appears in insert a of Fig. 10. In this case, as shown by the dotted line, stimulation caused an immediate local rise in temperature followed by a precipitous fall. There was a rise of smaller amplitude in the posterior cruciate gyrus followed by a small rebound to below its normal level. The rectal temperature showed an initial drop and started rising with a delay of about 1 min, and its increase was rather small as compared with the intracerebral changes.

After immobilization of the cat with 7 mg/kg gallamine (Flaxedil) it was possible to evoke a similar generalized electrical afterdischarge without motor convulsions, and the solid line of Fig. 10 shows that the
elicited thermal effects were less than in the normal animal, but were still evident and of greater amplitude in the stimulated orbital cortex than in the posterior cruciate gyrus, without affecting rectal temperature.

Controls
To test the possible heating of cerebral structures determined by the passage of current during experiments of electrical stimulation, the same intensity which induced a generalized seizure and a thermal increase in the brain, as shown in Fig. 10, was applied to the animal immediately after being sacrificed. No change of temperature could be detected in this case.

Histological analysis of the brain (Fig. 1) revealed implantation tracts of about 1 mm in diameter with a capsular reaction composed of neuroglia, microglia, fibroblasts, and collagen tissue. Beyond the capsule neuronal elements were normal in aspect with the exception of a few areas of demyelination extending occasionally up to 0.8 mm from the capsule.

Discussion
The assumption of authors such as Kawamura and Sawyer (26), Ogata (31), and Rampone and Shirasu (33) was that thermal recordings in any part of the brain reflected hypothalamic temperature and indicated a thermal homogeneity of the brain, but the findings of our experiments are in disagreement with these conclusions because a) spontaneous thermal variations in the motor cortex were different than in the hypothalamus (Fig. 2); b) petting affected temperature sooner in the amygdala than in the thalamus (Fig. 5 and ref. 12); c) electrical stimulation of the amygdala produced far greater shifts in the motor cortex than in the thalamus or hypothalamus (Fig. 9), whereas stimulation of the thalamus affected temperature in the reticular formation more than in the hypothalamus and motor cortex. These facts are in agreement with the data of Serota and Gerard (37) and Hardy and Hammel (22), which indicated that thermal recordings from one cerebral structure are valid only for this structure and cannot be considered representative of the whole brain.

In the studies of intracerebral temperature, it is therefore important to record simultaneously from several areas of the brain as we have done in our experiments. Although the hypothalamus is usually considered the main thermoreactive area of the brain, our experiments showed that the amygdala-pyriform region was in general more labile because this area had a greater number of spontaneous fluctuations (Fig. 3), its thermal changes during spontaneous and induced activities were of greater speed and amplitude than in the rest of the brain (Figs. 4 and 5), and during situations with emotional content determined by the presence of prey or the threat of an aggressive cat, the effect in the pyriform area was quicker and more pronounced than in other cerebral structures. Recently Keller and McClaskey (27) accepted the basic role of the hypothalamus for the neural integration of resistance to hypothermia but rejected its essentiality for the regulation of heat dissipation. In the analysis of the neuronal organization of thermoregulation, the hypothalamus should not be considered the only source of information.

To interpret thermal changes in the brain, we should remember that as Abrams and Hammel (1) stated, there are three factors related to the temporal modifications of intracerebral temperature: a) the production of
local heat by metabolic processes; b) the rate of local blood flow determined mainly by vasomotor adjustments; and c) the level of intraarterial temperature that reflects the general thermoregulatory processes of the organism.

It should be clarified that increases in blood flow may result in either a rise or drop in intracerebral temperature, depending on the relative thermal levels between brain and blood and as shown in Figs. 2 and 3, and in agreement with Feitelberg and Lamp1 (11), and Serota and Gerard (37), the hypothalamus and other cerebral areas may be warmer or cooler than the blood.

To interpret rises in intracerebral temperature as related to increased blood flow presupposes that the temperature is higher in the blood than in the brain, but this is a situation which must be verified experimentally and cannot be assumed because it is often untrue.

Abrams and Hammel (1) have stated that in the rat temperature changes in the arterial blood constituted the most important time-dependent parameter in determining temperature changes in the preoptic area, and in some of our experiments, for example in Fig. 6, the drop in intraarterial temperature preceded the intracerebral thermal fall. This, however, was the exception rather than the rule, and in many cases the fast changes in brain temperature proved relatively independent of the thermal level of the blood, indicating the importance of local factors.

Changes in local metabolic processes have been assumed to be the cause of changes in temperature. Serota (36) claimed that hypothalamic neurons decrease their metabolism during sleep, and Donhoffer et al. (10) have indicated that in the rat, exposure to cold may cause a local increase in heat production.

Unfortunately, most of the experimental evidence of changes in local metabolism related to temperature is only indirect, and in our studies we have only one more indirect proof, even if it seems rather clear. We are referring to the case in which amygdaloid stimulation induced a considerable thermal increase in the excited area and also in the posterior cruciate gyrus, whereas the intraarterial temperature decreased sharply (Fig. 9). The causal role of neuronal local metabolic factors seems to be evident here because of the complete thermal divergence between blood and brain.

It should be anticipated that induction of neuronal seizure activity would be accompanied by a sharp rise in local temperatures, and experimentation confirmed this expectation (Figs. 8 and 9). Also, it was logical to assume that neuronal paroxistic activity was the main cause of the local thermal rise, but the study under curare cast a
serious doubt on this possibility because electrical afterdischarges were evoked with a similar pattern in the curarized animal and in the normal animal, although the increase in temperature was considerably less in the last case (Fig. 10). Abolition of motor convulsions under curare may explain the inhibition of the cerebral thermal rise, but the mechanisms involved require further clarification. Can we accept that the missing element in animals under curare is the heat produced by muscular convulsions? If this were true, the body temperature in the convulsing normal animal should increase more and should be the cause of the rise in cerebral temperature, which was not the case; also, we must emphasize that the cerebral thermal increases during seizure activity affected specific cerebral structures, indicating that there was no general circulatory dependence.

As a working hypothesis, we may suppose that the local thermal rise produced during electrically evoked afterdischarges are related to three factors: a) increase in local neuronal activity; b) sensory feedback from contracting muscles that activates neuronal circuits within the brain; and c) local metabolic activity of neuroglia or other electrically silent structures. Curare would block only the last two factors. In addition, changes in cerebral blood flow should be taken into consideration because they have been detected during evoked seizures (16). Specialized thermal sensitivity should be located in deep structures such as the hypothalamus rather than in more superficial regions such as the motor cortex, because temperature of the brain surface was considerably affected by external factors, as shown in Fig. 7.

Most of the authors interested in brain temperature have described the drop which accompanied sleep (36), and recently Kawamura and Sawyer (26) have differentiated the thermal decline in the brain of rabbits observed during slow-wave sleep, from the rise recorded during fast-wave or paradoxical sleep. In our studies, we have confirmed the fall of temperature during slow-wave sleep and the rise during fast-wave sleep and, in addition, we have demonstrated the close correlation between electroencephalographic activity and brain temperature even in the absence of behavioral changes. Also it should be emphasized that the greatest changes in temperature when the cats awakened were recorded in the pyriform cortex and the smallest in the blood, indicating once more that the intracerebral thermal shifts were not dependent on the body temperature.

The administration of acetylcholine, adrenaline, and chlorpromazine in moderate doscs did not produce visible effects on brain temperature, and it was necessary to use high doses within toxic range in order to influence the cerebral temperature. Although the interest of these experiments is not considered physiological, they demonstrate that chlorpromazine and acetylcholine produced similar decreases in cerebral temperature, contrasting with the rises produced by adrenaline, and also proved the greater thermal activity of the amygdala compared with the hypothalamus under administration of drugs. Hoffman and Zarrow (24) also have described the rapid decline in body temperature in the rat and other animals following intramuscular injection of chlorpromazine (10 mg/kg).

The implications of thermal changes in the brain are not clear. They may be only secondary to metabolic and circulatory factors and without functional significance, but it is more probable that thermal changes represent an important factor in neuronal physiology affecting specialized unitary activity as demonstrated in the hypothalamus by Nakayama et al. (30). Our findings that, under electrical stimulation, functional correlations of temperature could be established between the amygdala and postcruciate gyrus and also between thalamus and reticular formation indicate that recordings of intracerebral temperature may be valuable tools to supplement electrophysiological analysis of relations among cerebral structures.

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