Cerebral cortex does not modulate "regulated" decrease in core temperature during hypoxemia in rats

EVVI-LYNN M. ROLLINS AND JAMES E. FEWELL
Department of Physiology and Biophysics, University of Calgary,
Health Sciences Centre, Calgary, Alberta, Canada T2N 4N1

Rollins, Evvi-Lynn M., and James E. Fewell. Cerebral cortex does not modulate "regulated" decrease in core temperature during hypoxemia in rats. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R1158–R1161, 1998.—In newborns and adults of a number of species including humans, exposure to acute hypoxemia produces a "regulated" decrease in core temperature, the mechanism of which is unknown. Considering that various cortical areas participate in autonomic regulation (3), including thermoregulation, the present experiments were carried out to test the hypothesis that the cerebral cortex plays a role in modulating the regulated decrease in core temperature during acute hypoxemia. This hypothesis was tested by determining the core temperature response to acute hypoxemia in chronically instrumented adult rats before and after cortical spreading depression (i.e., functional decortication) was produced by the local application of potassium chloride to the dura overlying the cerebral hemispheres. There was no effect of cortical spreading depression on baseline core temperature. Core temperature decreased during acute hypoxemia in a similar fashion when the cerebral cortex was intact as well as during functional decortication. Thus our data do not support the hypothesis that the cerebral cortex modulates the regulated decrease in core temperature that occurs in adult rats during acute hypoxemia.

cortical spreading depression; functional decortication

METHODS

Experiments were carried out on 29 male Sprague-Dawley rats (Charles River Breeding Laboratories, St.-Constant, PQ, Canada) weighing 216 ± 11 g on the day of surgery. The rats were housed in individual cages at 22 ± 1°C in a light-dark cycle with lights on from 0700 to 1900 and were handled at least five times before an experiment to familiarize the animal with the investigator. All animals had continuous access to food (Lab Diet 5001, St. Louis, MO) and tap water.

Surgical preparation. Each rat was anesthetized by an injection of pentobarbital sodium (65 mg/kg ip). A paramedian laparotomy was done, and a free-floating battery-operated biotelemetry device (PhysioTel TA10ETA-F20; Data Sciences International, St. Paul, MN) was inserted into the peritoneal cavity for later measurement of core temperature. The dorsum of the skull was then exposed and holes were drilled over both parietooccipital cortices using a 4-mm handheld trephine. Care was taken not to damage the dura and to achieve hemostasis. A polyvinyl chloride cylinder (15 mm in diam, 10 mm in height, with a screw cap) with a small flange was then placed within the skin margins and secured with one or two sutures. A piece of Parafilm was laid over the trephine holes, and a piece of filter paper, soaked in warm physiological saline, was placed in the cylinder. The cap was screwed onto the cylinder to protect the dura from drying and cooling. The animals were allowed to recover from surgery and were not studied before the 2nd postoperative day.

All surgical and experimental procedures were carried out in accordance with the "Guide to the Care and Use of Experimental Animals" provided by the Canadian Council on Animal Care, and with the approval of the Animal Care Committee of the University of Calgary.

Experimental apparatus. The experiments were carried out with the rats in a metabolic chamber that consisted of a double-walled Perspex cylinder (27 cm long, 7.5 cm ID) with a plastic grid along the bottom into which flowed room air or 10% O2 in N2 at 2.0 l/min. Chamber ambient temperature was controlled by circulating water from a temperature-controlled bath (Endocal Refrigerated Circulating Bath RTE-8DD; Neslab, Newington, NH) through the space between the walls. For measurement of core temperature, a thermocouple was placed over a platform antennae (PhysioTel CTR 86; Mini-Mitter, Sunriver, OR), which received the output frequency (Hz) from the biotelemetry device; this was interfaced with a peripheral processor (Dataquest III; Data

IN NEWBORNS AND ADULTS of a number of species including humans, core temperature decreases during acute hypoxemia (6, 24, 29). Gordon and Fogelson (17) and Dupre and Owen (10) have recently shown that the decrease in core temperature during acute hypoxemia in adult rats is a "regulated" rather than a "forced" phenomenon (16) and thus represents an example of "homeostasis" (30), or regulation around a shifted set point, rather than a failure of "homeostasis" (2). The mechanism of this regulated decrease in core temperature during acute hypoxemia is not known.

Numerous mechanisms have been suggested to elicit the regulated decrease in core temperature during acute hypoxemia. These include a direct effect hypoxemia on thermosensitive neurons in the preoptic area of the anterior hypothalamus (39) as well as the release of various peptides in the central nervous system [e.g., arginine vasopressin (44) and endogenous opioids (26)] that influence thermoregulation. Furthermore, because numerous experiments have provided evidence that various cortical areas participate in autonomic regulation (3), including thermoregulation, it is also possible that the cerebral cortex plays a role in modulating the regulated decrease in core temperature during acute hypoxemia. Thus the purpose of the present experiments was to test the hypothesis that the cerebral cortex plays a role in modulating the regulated decrease in core temperature during acute hypoxemia. This hypothesis was tested by determining the core temperature response to acute hypoxemia in chronically instrumented adult rats before and after cortical spreading depression (i.e., functional decortication) as first described by Leao (22) was produced by the local application of potassium chloride to the dura overlying the cerebral hemispheres.

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Sciences International, St. Paul, MN) connected to an IBM computer.

Experimental protocol. The rats were studied at an ambient temperature of either 27 ± 1°C (i.e., thermoneutral temperature) or 18 ± 1°C. Each animal was randomly assigned to either a normoxemic or hypoxemic group and underwent two experiments on successive days. One experiment was carried out during "functional decortication" produced by cortical spreading depression, and one experiment was carried out with the rat’s cerebral cortex intact; the sequence of the two experiments was alternated between animals.

On the day of an experiment, each rat was brought into the laboratory and weighed. To ensure that there was no postoperative damage to the dura or underlying structures, the animals were then tested for the presence or absence of bilateral visual and tactile placing reactions (1). If bilateral visual and tactile placing reactions were present, the rat was then placed into the metabolic chamber for 1 h. After collection of control data, the rats were taken out of the metabolic chamber, and a filter paper soaked with either potassium chloride or normal saline was applied to the dura. The rats were returned to the chamber for 10 min and then removed once more and tested for the presence or absence of bilateral visual and tactile placing reactions. The rat was then returned to the chamber. After 30 min, the O2 mixture flowing into the chamber was either left at 21% or changed to 10%, and data were collected at 6-min intervals for the next 60 min. At the end of each experiment, the animal was tested once again for the presence or absence of bilateral visual and tactile placing reactions.

Cortical spreading depression. Application of depolarizing chemicals (e.g., K+; Ref. 23) to the cortex of rats induces so-called spreading depression (i.e., a slowly spreading wave of neural depolarization and depression of electroencephalographic activity, which traverses cortex at a rate of ∼3 mm/min and lasts ∼2 min). The presence of a hypertonic potassium chloride solution in contact with the cortex will lead to repetitive waves of spreading depression and thus a long-lasting depression of electroencephalographic activity; this constitutes functional decortication (1).

Statistical analysis. Statistical analysis was carried out using a four-factor ANOVA for repeated measures followed by a Student-Newman-Keuls multiple comparison test to determine whether ambient temperature, time, state of cortex, or gas mixture affected core temperature (43).

RESULTS
Core temperature decreased during acute hypoxemia when the cerebral cortex was intact as well as during functional decortication (Fig. 1); the overall response was accentuated when the animals were studied at 18°C compared with 27°C (ambient temperature by gas mixture, P = 0.001). There was no effect of cortical spreading depression on baseline core temperature or on the core temperature response to hypoxemia at either ambient temperature (state of cortex, P = 0.568; state of cortex by ambient temperature, P = 0.590; state of cortex by gas mixture, P = 0.241; state of cortex by ambient temperature by gas mixture, P = 0.536). Exposure to acute hypoxemia produced an initial period of excitement, which was followed by a period of quiescence; this response was not affected by functional decortication.

DISCUSSION
Our experiments provide new information regarding possible mechanisms underlying the regulated decrease in core temperature during acute hypoxemia in adult rats. A novel finding in our study was that the decrease in core temperature during acute hypoxemia was not influenced by functional decortication induced by cortical spreading depression. Thus our data do not support the hypothesis that the cerebral cortex modu-
lates the regulated decrease in core temperature during acute hypoxemia in adult rats.

A number of experiments, both anatomical and physiological in nature, have provided evidence that various cortical areas are involved in autonomic function (3). For example, experiments carried out in the 1930s and 1940s showed that surgical decortication impaired the ability of dogs, cats, and monkeys to thermoregulate when they were exposed to hot or cold environments (7, 32). Moreover, recent experiments utilizing the technique of cortical spreading depression have shown that functional decortication in rats inhibits warm-sensitive neurons and facilitates cold-sensitive neurons in the preoptic area of the hypothalamus as well as increasing both metabolic heat production and operant skin heating behavior and reducing operant skin cooling behavior (33, 34, 36). The area responsible for this thermoregulatory behavior appears to be the sulcal prefrontal cortex, a site of convergence of skin and hypothalamic temperature signals (35) and a site known to have projections to the hypothalamic thermosensitive neurons (18, 19). DeLuca et al. (8) have shown that electrical stimulation of the prefrontal but not the parietal or occipital cortex increases metabolic rate through activation of the sympathetic nervous system. Shibata et al. (35) have suggested that sulcal prefrontal cortical neurons play a role in processing and integrating thermal signals arising from different parts of the body, probably in connection with the emotional and/or motivational aspect of neural sensation and thermoregulatory behavior.

Cortical spreading depression did not significantly affect baseline core temperature in our experiments; this was true when the rats were studied in an ambient temperature of 30 °C or below thermoneutrality. Our data are in keeping with the results of DeLuca et al. (9), Monda and Pittman (28), and Monda et al. (27) but differ from the results of Shibata et al. (36, 37) and Hori et al. (19), who found that cortical spreading depression activated thermoregulatory effectors to increase core temperature. Although the reason for these differences is not readily apparent, it may be related to the strain of rats used, since the former investigators used Sprague-Dawley rats, whereas the latter investigators used Wistar rats. The differences are not related to gender, since both male and female Sprague-Dawley rats were used in the former investigations.

Previous experiments carried out in our laboratory as well as in the laboratories of others have provided information about possible mechanisms underlying the regulated decrease in core temperature during acute hypoxemia. For example, experiments carried out on conscious guinea pigs (11), rats (13, 15, 25), and cats (14) have provided evidence that the carotid chemoreceptors and/or baroreceptors are not essential for the decrease in core temperature to occur during acute hypoxemia. In fact, because core temperature and O2 consumption decrease more in carotid-denervated than in carotid-intact animals, it appears that the carotid chemoreceptors and/or baroreceptors actually buffer or moderate the changes in these variables during acute hypoxemia.

Wood (44) has suggested that an increase in central levels of arginine vasopressin may mediate the changes in core temperature observed during hypoxemia. Evidence to support this hypothesis is provided by the following. Hypoxemia stimulates the release of arginine vasopressin into plasma (12) and cerebrospinal fluid (38, 42) of animals; intracerebroventricular administration of arginine vasopressin elicits hypothermia in rats (20, 21, 31); arginine vasopressin is an endogenous antipyretic peptide in mammals (5, 41). Conversely, our experiments on core temperature responses to hypoxemia in Long-Evans (which have arginine vasopressin-containing cells in central nervous system) and Brattleboro rats (which lack arginine vasopressin-containing cells in central nervous system; Ref. 40) do not support this hypothesis, since core temperature decreases more in Brattleboro rats during both moderate and severe hypoxemia than in Long-Evans rats (4).

Mayfield et al. (26) have recently provided evidence that endogenous opioids participate in mediating the decrease in core temperature after hypoxic conditioning in adult mice. In their experiments, however, hypoxic conditioning, which consisted of exposing adult mice to 4.5% O2 for 1.5, 2.0, and 2.5 min separated by 5 min of 21% O2, produced sustained decreases in core temperature. These sustained decreases in core temperature after return to normoxemia, which are in contrast to previous results obtained in our laboratory (4), most likely resulted from the severe degree of hypoxemia used during their hypoxic conditioning. In our view, the role that endogenous opioids play in mediating the decrease in core temperature to a moderate level of acute hypoxemia remains unknown. Other possible mediators of the regulated decrease in core temperature during hypoxemia include histamine, adenosine, and α-melanocyte-stimulating hormone. The influence of these agents requires further investigation.

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Address for reprint requests: J. E. Fewell, Heritage Medical Research Bldg. 206, University of Calgary, 3330 Hospital Dr., NW, Calgary, AB, Canada T2N 4N1.

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