Anesthesiology
75:557–559, 1991

Central Thermoregulatory Inhibition by General Anesthesia

HUMANS REGULATE TEMPERATURE by comparing thermal inputs from the skin surface,[1] neuraxis,[2–4] and deep abdominal and thoracic tissues[5,6] with *threshold* temperatures. When the integrated thermal input exceeds the warm-response thresholds, sweating and active capillary vasodilation are initiated in an effort to prevent further hyperthermia. Similarly, a body temperature lower than the cold-response thresholds triggers arteriovenous shunt vasoconstriction, nonshivering thermogenesis, and shivering, which work to minimize further hypothermia. The rate at which response intensity increases as body temperature progressively deviates from a triggering threshold is the *thermosensitivity* (gain) of that response. At some point, each response reaches its *maximum*, and further deviation from the threshold temperature produces no increase in response intensity.[7] The difference between the lowest warm and the highest cold threshold temperatures is the *interthreshold range;* typically it is $\approx$ 0.4° C. Thermoregulatory responses do not occur within this range, even though humans can detect temperature changes as small as 0.003° C.[8]

Clinical studies indicate that general anesthesia does not simply produce global thermoregulatory impairment: the impairment has a specific pattern. Volatile anesthetics produce dose- and agent-dependent decreases in the thresholds for vasoconstriction, shivering, and (in infants) nonshivering thermogenesis.[9–11] Conversely, general anesthesia increases threshold temperatures triggering sweating and active vasodilation.[12] The result is a ten-fold increase in the interthreshold range, to $\approx$4° C. Despite the marked decrease in the activation threshold for vasoconstriction, the thermosensitivity and maximum intensity of this response appear to be well-preserved.[10,13] Similarly, the thermosensitivity and maximum intensity of sweating, active vasodilation, and nonshivering thermogenesis also remain essentially intact during general anesthesia.[14,*]

Engineering analogs such as *threshold* and *thermosensitivity* are useful for describing observed thermoregulatory responses and predicting their intensities under a variety of circumstances. However, it is known that physiologic processing of thermal input and control of regulatory responses is far more complicated than these models suggest.[15–17] Satinoff has proposed a hierarchical system in which signals are successively processed in the spinal cord, midbrain, and hypothalamus.[18] In this system, phylogenetically "older" centers subserve "newer" and more precise regulatory systems. Because the hypothalamus is dominant, its responses to thermal perturbations are of particular interest. In this issue of ANESTHESIOLOGY, Poterack and co-workers report firing rates of single cells in the preoptic region of the hypothalamus.[19]

The authors recorded firing rates of warm-sensitive hypothalamic neurons in cats anesthetized with chloralose and urethane. (Six cold-sensitive cells also were identified, but recordings were completed only in one.) The spontaneous firing rate and thermosensitivity of twenty-one neurons were recorded during administration of 0, 0.25, 0.5, 0.75, and 1.0% end-tidal halothane concentrations. Neuronal spontaneous firing rate decreased linearly to 18% of control values as halothane concentration was increased to 1.0%. However, thermosensitivity *increased* 16% at 0.25% halothane (although the increase was not statistically significant) and then decreased markedly, to $<$ 35% of control values, at the higher halothane concentrations. Hypothalamic heating and cooling in the absence of halothane did not produce consistent changes in electroencephalographic patterns.

An inherent limitation of single-cell recordings is that even ambitious studies evaluate a relatively small number of thermosensitive units. Moreover, as in this study,[19] cold-responsive cells typically are a small fraction of the total number identified.[20] Clinicians might argue that in the perioperative period, responses to hypothermia are more important than responses to elevated temperature. In addition, the invasive nature of central electrophysiologic studies prohibits their being undertaken in humans. Fortunately, thermoregulatory processing is similar in most mammals.

More importantly, background anesthesia was required for Poterack, Kampine, and Schmeling's study. Although chloralose and urethane are believed to cause less thermoregulatory inhibition than halothane,[21] rats given urethane become poikilothermic.[22] Urethane further differs from volatile anesthetics by impeding thermoregulatory response efficacy while leaving thresholds relatively unchanged.[22] At the very least, background anesthesia in this study[19] obscured the electroencephalographic changes normally accompanying thermal challenge.[23,24]

Electrophysiologic techniques are limited also by the

Accepted for publication June 30, 1991.

Address reprint requests to Dr. Sessler: Department of Anesthesia, University of California, San Francisco, California 94143-0648.

Key words: Temperature: regulation.

* Unpublished data.

difficulty in extrapolating data from a few localized cells to observed responses in intact organisms. Among physiologists studying thermoregulation, concern about such extrapolations is heightened by the increasing recognition that hypothalamic temperature *per se* provides a relatively small fraction (perhaps only 20%) of total thermal input.[2] Thus, while the hypothalamus remains the dominant thermoregulatory site in mammals, its own temperature sensitivity appears modest and may be mechanistically separate from its major function—the orchestration of responses to distant thermal sensors. It is likely that many thermoregulatory interneurons are not themselves temperature-sensitive and consequently would not have been tested in this study. Regulatory cells might better have been identified by their response to isolated thermal manipulations at a distant site.[25] Only 1 of the 21 neurons that were sensitive to hypothalamic warming in this study[19] also responded to spinal cord warming.

Unfortunately, Poterack, Kampine, and Schmeling did not correlate their intriguing observations with physiologic responses such as vasoconstriction and sweating. Consequently, it is not possible to link their electrophysiologic data with systemic response thresholds, thermosensitivities, and maximum intensities. However, the authors' data add a valuable dimension to clinical studies by localizing a direct temperature-dependent effect of halothane.

Evidence that halothane produces dose-dependent inhibition of warm-responsive hypothalamic neurons, *and* the assumption that these neurons are thermoregulatory, help identify mechanisms by which general anesthesia produces thermoregulatory inhibition. The progressive decrease in the spontaneous firing rate of warm-sensitive hypothalamic neurons during general anesthesia resembles the clinically observed dose-dependent increase in the thresholds for sweating and active vasodilation. These data suggest that anesthetic-induced threshold alterations may be directly mediated (at least in part) by thermosensitive hypothalamic neurons.

In contrast to the marked changes in threshold temperatures produced by halothane anesthesia, thermosensitivities and maximum response intensities remain relatively well-preserved in clinical studies.[10,13,14,*] It is difficult to reconcile this preservation with the profound decrease in spontaneous firing rate and thermosensitivity of hypothalamic neurons reported by Poterack and coworkers.[19] Although thermosensitivity might be mediated by nonthermosensitive hypothalamic neurons, rabbits with acute cervical transections respond to spinal cord heating and cooling with a broadened interthreshold range.[26] (In animals with only ventrolateral funiculi transection[27] and in chronic T5–T8 preparations,[28] shivering intensity and pattern are virtually normal.) These data suggest that thermosensitivity and maximum response intensity may be mediated largely by centers below the hypothalamus.

In summary, inherent experimental limitations make it difficult to extrapolate mechanisms of thermoregulatory control from single-cell recordings. Nonetheless, elegant data presented by Poterack and coworkers[19] add a valuable dimension to clinical studies indicating that general anesthesia increases the interthreshold range approximately ten-fold while leaving thermosensitivity and maximum intensities of thermoregulatory responses relatively intact. These observations are consistent with a system in which critical thresholds are determined largely in the hypothalamus and are profoundly inhibited by general anesthesia. In contrast, thermosensitivities and maximum response intensities (which might be considered "mechanical details") may be mediated by lower centers whose functions remain nearly intact during anesthesia.

DANIEL I. SESSLER, M.D.
Assistant Professor of Anesthesia
Department of Anesthesia
University of California
San Francisco, California

References

1. Benzinger TH, Pratt AW, Kitzinger C: The thermostatic control of human metabolic heat production. Proc Natl Acad Sci USA 47:730–739, 1961
2. Simon E: Temperature regulation: The spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev Physiol Biochem Pharmacol 71:1–76, 1974
3. Kosaka M, Simon E, Walther O-E, Thauer R: Response of respiration to selective heating of the spinal cord below partial transection. Experientia 25:36–37, 1969
4. Chai CY, Lin MT: Effects of heating and cooling the spinal cord and medulla oblongata on thermoregulation in monkeys. J Physiol (Lond) 225:297–308, 1972
5. Mercer JB, Jessen C: Central thermosensitivity in conscious goats: Hypothalamus and spinal cord versus residual inner body. Pflügers Arch 374:179–186, 1978
6. Riedel W, Siaplauras G, Simon E: Intra-abdominal thermosensitivity in the rabbit as compared with spinal thermosensitivity. Pflügers Arch 340:59–70, 1973
7. Sessler DI: Temperature monitoring, Anesthesia. 3rd edition. Edited by Miller RD. New York, Churchill Livingstone, 1990, pp 1227–1242
8. Hardy JD, Oppel TW: The thermal response of the skin to radiation. Physics 7:466–479, 1936
9. Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ: The thermoregulatory threshold in humans during halothane anesthesia. ANESTHESIOLOGY 68:836–842, 1988
10. Støen R, Sessler DI: The thermoregulatory threshold is inversely proportional to isoflurane concentration. ANESTHESIOLOGY 72: 822–827, 1990
11. Bissonnette B, Sessler DI: The thermoregulatory threshold in infants and children anesthetized with isoflurane and caudal bupivacaine. ANESTHESIOLOGY 73:1114–1118, 1990
12. Sessler DI: The sweating threshold during isoflurane anesthesia in humans. Anesth Analg, in press

13. Sessler DI, Moayeri A, McGuire J, Hynson J: Vasoconstriction during general anesthesia minimally decreases cutaneous heat loss (abstract). ANESTHESIOLOGY 73:A212, 1990
14. Washington D, Sessler DI, Prager M, McGuire J, Merrifield B, Hudson S, Moayeri A: Dose-response for thermoregulatory sweating threshold and gain during isoflurane anesthesia (abstract). ANESTHESIOLOGY 75:A194, 1991
15. Amini-Sereshki L, Zarrindast MR: Brain stem tonic inhibition of thermoregulation in the rat. Am J Physiol (Lond) 247:R154–R159, 1984
16. Fuller CA, Horowitz JM, Horwitz BA: Spinal cord thermosensitivity and sorting of neural signals in cold-exposed rats. J Appl Physiol 2:154–158, 42
17. Baldwin BA, Ingram DL: The effect of heating and cooling the hypothalamus on behavioural thermoregulation in the pig. J Physiol (Lond) 191:375–392, 1967
18. Satinoff E: Neural organization and evolution of thermal regulation in mammals: Several hierarchically arranged integrating systems may have evolved to achieve precise thermoregulation. Science 201:16–22, 1978
19. Poterack KA, Kampine JP, Schmeling WT: The effect of halothane on thermosensitive neurons in the preoptic region of the anterior hypothalamus in acutely instrumented cats. ANESTHESIOLOGY 75:625–633, 1991
20. Baldino F Jr, Beckman AL, Adler MW: Actions of iontophoretically applied morphine on hypothalamic thermosensitive units. Brain Res 196:199–208, 1980
21. Ingram DL, Smith REL: Brain temperature and cutaneous blood flow in the anesthetized pig. J Appl Physiol 29:698–704, 1970
22. Malkinson TJ, Cooper KE, Veale WL: Physiological changes during thermoregulation and fever in urethan-anesthetized rats. Am J Physiol 255:R73–R81, 1988
23. Glotzbach SF, Heller H: Central Nervous regulation of body temperature during sleep. Science 194:537–539, 1976
24. Grahn DA, Radeke CM, Heller HC: Arousal state *vs.* temperature effects on neuronal activity in subcoeruleus area. Am J Physiol 256:R840–R849, 1989
25. Boulant JA, Hardy JD: The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. J Physiol (Lond) 240:639–660, 1974
26. Kosaka M, Simon E, Thauer R: Shivering in intact and spinal rabbits during spinal cord cooling. Experientia 23:385–387, 1967
27. Klußmann FW: Energy production of rabbits before and after transection of both ventro-lateral funiculi of the spinal cord. J Thermal Biol 8:133–135, 1983
28. Herdman SJ: Recovery of shivering in spinal cats. Exp Neurol 59: 177–189, 1978