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Postanesthetic Shivering in Primates: Inhibition by Peripheral Heating and by Taurine

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There has been little research on the cause(s) of postanesthetic shivering (PAS) and on specific interventions. Therefore, the authors investigated PAS in eight unoperated squirrel monkeys anesthetized with halothane–nitrous oxide mixture. Shivering developed in all monkeys in which body temperature was allowed to decrease (mean ± SEM, 2.8 ± 0.6° C) during anesthesia. Shivering occurred in 25% of animals in which body temperature was actively maintained at preanesthetic levels during anesthesia. No shivering occurred in animals warmed both during and after anesthesia. Application of radiant heat to the skin stopped PAS immediately, even though deep body temperature remained low; shivering resumed within seconds after this heating was discontinued. Intracerebroventricular (0.1–2 mg) and intravenous (100 mg/kg) administration of the putative inhibitory neurotransmitter taurine also stopped the shivering in preliminary experiments, but central injection of α-melanocyte stimulating hormone (100–300 μg), an endogenous antipyretic, did not. The results implicate reduced body temperature and activation of central heat production pathways as major factors in PAS and suggest that halothane–nitrous oxide anesthesia *per se*, elevation of the thermal set-point, and surgical procedures are not essential to the shivering phenomenon. The results suggest for future study two methods to control PAS: application of radiant heat or administration of taurine. (Key words: Anesthetics, volatile: halothane. Hypothermia: shivering. Neurotransmitters: taurine. Temperature: regulation.)

POSTANESTHETIC SHIVERING (PAS) is a well-known clinical phenomenon. The potential deleterious effects of PAS include a marked increase in cardiopulmonary activity required to supply extra oxygen for shivering, development of metabolic acidosis, and damage to operated tissues. Severe thermal discomfort is also part of the PAS syndrome, and this intense sensation of cold is a frequent postoperative complaint. A number of possible causes have been considered, including specific anesthetic agent(s), anesthetic technique, duration of anesthesia, decrease in body temperature, increase in the central thermoregulatory set-point, alteration of central nervous system (CNS) activity, pyrogen release and patient age, body weight, and sex characteristics.[1–7,¶] However, there has been little research on the determinants of PAS in the absence of surgery and when specific physiologic or pharmacologic variables are controlled. Our experiments on a subhuman primate model were designed to determine the following: 1) if shivering occurs after halothane–nitrous oxide anesthesia in this species; and, if so, 2) if the mechanism of PAS can be determined; 3) if stimulation of peripheral warm receptors alone can inhibit PAS, and 4) if taurine or α-melanocyte-stimulating hormone (α-MSH), putative neurotransmitters that are known to alter thermoeffector activity, can inhibit PAS.

Materials and Methods

ANIMALS

Eight adult male squirrel monkeys (*Saimiri sciureus*), 800–1,100 g, were used. They were maintained on monkey biscuits (Wayne, Allied Mills, Inc.) and fruit; water was available *ad libitum*. The animals were individually caged in a 23–25° C environment with a 12-h light/dark cycle. All experiments were performed during the light phase in a thermoneutral environment (24 ± 1° C) and were initiated at approximately the same time each experimental day.

CANNULA IMPLANTATION

Four monkeys were pretreated with ketamine hydrochloride (2–3 mg, im), atropine sulfate (0.02 mg/kg, im) and anesthetized with sodium pentobarbital (15 mg/kg, ip). Each animal was placed in a Kopf stereotaxic instrument designed for the species, and a cannula (David Kopf Instruments, No. 201) was implanted aseptically into a lateral cerebral ventricle with the use of coordinates (6.0 mm anterior, 3.0 mm lateral, vertical until cerebrospinal fluid appeared in the cannula) derived from the atlas of Emmers and Akert.[8] Dental acrylic was used to secure the cannula to stainless-steel screws driven into the calvarium. Experiments were not begun for at least 2 weeks after implantation.

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¶ Flacke JW, Flacke WE: Inadvertent hypothermia: frequent, insidious, and often serious. Seminars in Anaesthesia 2:183–196, 1983.

TABLE 1. Rectal Temperature and Postanesthetic Shivering Incidence in Halothane/Nitrous Oxide Anesthetized Squirrel Monkeys in which Body Temperature Was Allowed to Decrease (Group 1) or Was Maintained only During Anesthesia (Group 2) or Both during and after Anesthesia (Group 3). Ambient Temperature 24 ± 1.0° C

	Rectal Temperature (°C)		Number of Animals	
	Preanesthesia	Postanesthesia	Shivered	Total
Group 1	38.7 ± 0.4	35.9 ± 0.7	8	8
Group 2	38.5 ± 0.6	38.9 ± 0.5	2*	8
Group 3	39.0 ± 0.4	39.6 ± 0.6	0*	6

* Significantly different ($P < 0.01$) from Group 1.

PHYSIOLOGIC MEASUREMENTS

Rectal (10 cm insertion) and skin (dorsal surface of the base of the tail) temperatures were recorded continuously with the use of probes (Yellow Springs International nos. 401 and 409, respectively) connected to telethermometers (YS1 model 43). Electrical activity of the thigh muscle (EMG) was recorded with the use of a dual-needle electrode assembly designed for the purpose. Two platinum EEG electrodes were fixed 8 mm apart, and the assembly was inserted into the belly of the right hamstring muscle. Heart rate and rhythm were recorded via ECG electrodes attached to the chest. The temperature, EMG, and ECG data were recorded with a Grass® Instruments polygraph (model 7) equipped with an integration channel for EMG activity. Respirations were counted for 20 s every 5 min throughout the procedure.

TREATMENTS AND INJECTIONS

No preanesthetic agents were administered. Anesthesia was induced with halothane via a pediatric face mask while the animals were restrained in standard primate chairs. The monkeys' tracheas were intubated (2.0 mm endotracheal tube) and maintained on 2% inspired halothane carried by N_2O and oxygen (2:1) for 30 min. Ventilation was spontaneous. Anesthetic gases were then discontinued, and the animals were maintained on oxygen until gagging or coughing occurred, whereupon the endotracheal tube was removed. Body temperature was allowed to passively fall during anesthesia in one group of studies (Group 1). An infrared heat lamp (250 W) and/or an electrical heating pad were used to maintain preinduction body temperature during anesthesia in another group (Group 2) and both during and after anesthesia in a third group (Group 3).

In subsequent studies, four animals received either taurine, α-MSH or saline immediately after discontinuance of the anesthetic gases or after shivering had begun. Taurine and α-MSH were dissolved in 0.9% normal saline and injected intracerebroventricularly (icv) via the indwelling cannula (50 μl volume + 20 μl saline flush). Taurine was also administered via the lateral tail vein. In control experiments unanesthetized animals were placed in restraining chairs designed for the species and tested in an environmental chamber maintained at 24 ± 1° C.

EXPERIMENTAL DESIGN AND DATA ANALYSIS

All eight monkeys received the three treatments (Groups 1–3) separated by at least 3 days and according to random assignment of treatment order. Each animal served as its own control. Shivering was defined as periodic regular contractions involving major muscle groups, including the thigh muscles. Fasciculations of the face and neck alone were disregarded. Abolition of shivering was determined both visually and via the EMG record. Because of absolute differences in the amplitude of the EMG signals measured at slightly different sites, on different days, and in different animals, no attempt was made to determine partial reduction or to quantify the degree of shivering. Rather, an "all or nothing" protocol was used, and we simply recorded the presence or absence of shivering over time. Fisher's exact probability test was used for statistical analysis of the data.

Results

All eight animals shivered after body temperature was allowed to decrease (mean, 2.8° C; range 1.9 to 3.6° C) during halothane–nitrous oxide anesthesia (Group 1; table 1). The shivering was characteristic in gross electrographic appearance of cold-induced shivering noted in previous research on the same[9] and on other[10] species, and in man.[11] PAS began 4.5 ± 0.4 min after removal of the gases and continued for approximately 15 to 30 min. Two of eight animals in which deep body temperature was artificially maintained at preinduction levels during anesthesia shivered after halothane–nitrous oxide and the heat source were withdrawn (Group 2). None of these eight monkeys shivered when external heating was maintained both during and after anesthesia (Group 3).

Shivering ceased immediately after a heat lamp was directed upon each of the hypothermic animals in Group 1, even though no change occurred in the low core temperature (fig. 1). PAS resumed within 1.5 s after the lamp was removed. In addition, on some occasions in which tracheal intubation took longer than usual, shivering was noted as the anesthetic effect waned, even though no decrease in core temperature was observed. This shivering stopped when inhalation of the anesthetic gases was resumed.

In separate experiments, repeated icv injection of 100–300 μg of the centrally acting endogenous antipyretic neuropeptide α-MSH or of saline had no effect on shivering onset in any of the four animals tested (fig.

2). On the other hand, central injection of the sulfonated inhibitory neurotransmitter taurine (0.1–2 mg) consistently delayed the onset of shivering (6.3–12.2 min; n = 4) and abolished ongoing PAS within 30 s (n = 4; shivering resumed 5.6–19.4 min later) in a dose-related fashion. Intravenous administration of taurine (100 mg/kg) likewise abolished PAS in all four of the hypothermic animals tested. Doses of taurine that inhibited shivering (2 mg icv, N = 4; 100 mg/kg iv, n = 4) had no effect on normal body temperature when given to unanesthetized animals.

Discussion

Postanesthetic shivering has been recognized for many years in the medical literature and has been variously named: ether convulsions, halothane shakes, postoperative spasms, or rigidity and postanesthetic shivering. PAS can be dangerous in patients with limited cardiovascular and respiratory function, and myocardial infarction has been associated[12] with the marked increase in oxygen demand and with the hypoxemia that can occur with PAS.[3,13,14] Study of the precise cause of PAS in humans is limited by obvious constraints on possible interventions and the lack of control (nonsurgery) data during and after human anesthetic procedures.

For this study we selected the squirrel monkey, a primate species previously shown to have thermoregulatory responses and sensitivity to pyrogen similar to those of humans.[9,15] The animals responded to halothane/nitrous oxide anesthesia with hypothermia, and they reliably developed PAS that was similar in major respects to that seen in humans. These findings suggest that the squirrel monkey is a suitable model for this type of research.

Possible mechanisms for PAS can be divided into three categories: 1) direct effects of the anesthetic agent (*e.g.*, specific type, technique or duration of anesthesia, change in the central set-point of temperature control, alteration of CNS activity, development of acute abstinence syndrome); 2) effects secondary to anesthesia (*e.g.*, stimulation of endogenous pyrogen release, hypothermia); and 3) factors unrelated to anesthesia (*e.g.*, type or duration of surgery, pyrogen release during tissue destruction, individual patient characteristics). Our data can be considered in terms of the first two categories; the experiments were designed to control for the third group of factors.

Concerning the role of halothane–nitrous oxide in the genesis of PAS, the finding that shivering generally occurred in all animals in which temperature was allowed to decrease but in only two animals in which the temperature was actively maintained within the normal range suggests that factors directly related to the anesthetic are not primary causes of PAS, since both groups received halothane–nitrous oxide. Clinical surveys also support this concept, reporting an incidence of shivering between 5 and 37%[2,3] after halothane, rather than 100%.

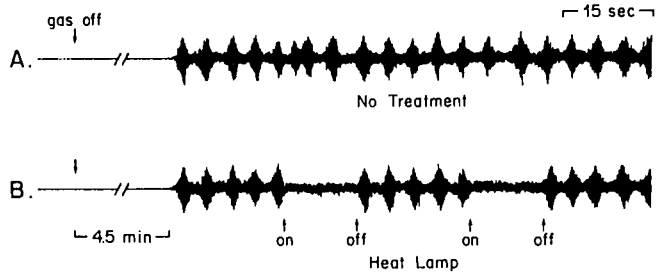

FIG. 1. Effect of peripheral heat on shivering after discontinuance of halothane–nitrous oxide anesthesia ("gas off") in a single monkey. *A.* Control PAS with no peripheral heating. *B.* Immediate cessation of shivering in response to heat and reinstatement of PAS when heat is turned off.

To test the possibility that halothane–nitrous oxide increases the central set-point of temperature control via release of endogenous pyrogens, we administered the naturally occurring, centrally acting antipyretic substance α-MSH.[16,17] This peptide, given at doses greater than those required to inhibit fever, had no effect on PAS. Also, shivering gradually diminished and then ceased in each animal as its core temperature approached the pretest level. With a direct elevation of the thermal set-point, the shivering would have continued until body temperature reached the new, higher value. We conclude from these results that PAS does not depend upon

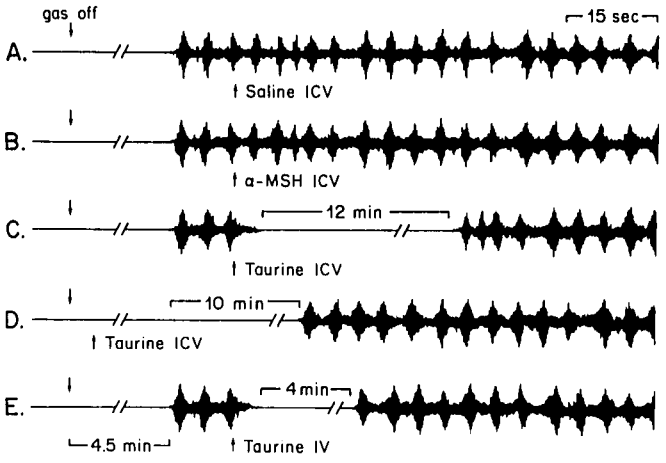

FIG. 2. Effects of saline, α-MSH, and taurine on PAS in monkeys that were hypothermic after halothane–nitrous oxide. Discontinuance of anesthetic at "gas off." *A.* Saline given icv did not affect PAS. *B.* α-MSH (300 μg) icv did not alter shivering. *C.* Taurine (2 mg icv) given after shivering had begun inhibited PAS. *D.* Taurine (2 mg icv) given before PAS began delayed the onset of shivering. *E.* Taurine given iv (100 mg/kg) inhibited PAS.

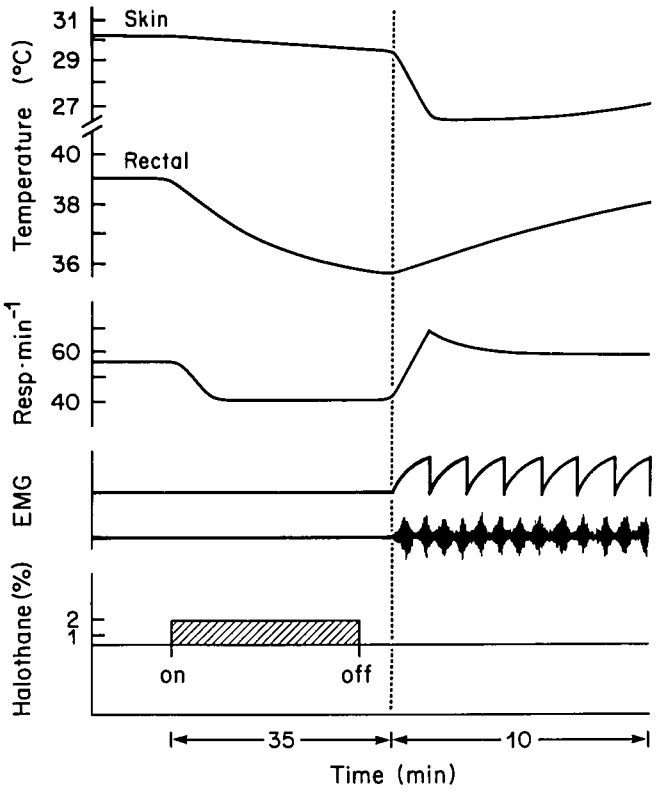

FIG. 3. Physiologic changes associated with halothane inhalation in a representative monkey in which core temperature was allowed to decrease. Exposure to halothane/nitrous oxide anesthesia for 30 min caused a decrease in rectal temperature of almost 3° C. Within 5 min after discontinuance of anesthesia, shivering began (EMG: lower trace, analog of shivering burst; upper trace, integration of EMG activity during shivering). Vasoconstriction (decrease in skin temperature) also occurred and respiration rate increased.

alteration of the thermal set-point either directly or secondarily via release of endogenous pyrogens by the anesthetic.

Since shivering occurred regularly in cold but not in warmed animals, the simplest explanation of our results seems to be that PAS resulted primarily from cold thermal stimulation of central heat gain mechanisms, both heat production (shivering) and heat conservation (vasoconstriction) (fig. 3). The extent to which this holds for human PAS is not clear, in large part because of the many uncontrolled variables. Jones and McLaren[3] as well as Moir and Doyle,[2] reported lower temperature in shivering patients, whereas others[4,5] have found no difference in body temperature between shivering and nonshivering hypothermic patients. Bourke *et al.*,[18] using warming pads and reflective blankets, observed shivering even in patients whose body temperature during surgery increased above preanesthetic levels.

Since shivering occurred in two of the eight animals warmed during but not after anesthesia, and in a few instances when the effects of the mask induction began to wane during lengthy intubation, it is possible that slowed metabolism resulted in a decrease in heat content in some body region[19] that was sufficient to induce shivering, without causing a measurable decrease in rectal temperature.

Horvath *et al.*[14] noted that shivering onset and generalized shivering in nude male subjects exposed to cold was associated with an increase rather than a decrease in core temperature. These authors concluded that shivering was stimulated by reduced skin temperature following a shift in blood from periphery to core, and this may explain the shivering in 25% of the monkeys in which rectal temperature was maintained by peripheral heat during anesthesia, since the effective skin temperature decreased markedly upon removal of the external heat source after anesthesia.

The inhibition of PAS by central and peripheral injections of taurine was remarkable. This sulfur-containing inhibitory neurotransmitter inhibits central heat production and conservation pathways.[20,21] In the present experiments taurine both delayed the onset of PAS and inhibited ongoing PAS. These data suggest that the effector mechanisms involved in PAS include activation of those central heat production pathways that are utilized in fever and in response to cold and that are known to be inhibited by taurine. This finding raises the possibility that taurine may be useful in controlling PAS in humans.

The differences in shivering incidence between the temperature controlled and noncontrolled animals cannot be considered absolute evidence against a direct influence of halothane–nitrous oxide, since peripheral warming has a powerful inhibitory effect on PAS. Such an inhibition may prevent shivering due to any cause. This is consistent with the results of Cabanac *et al.*[22] and of Penrod,[23] who described the overriding effect of skin warming on shivering in cold animals. The rapid cessation of shivering caused by stimulation of cutaneous warm receptors via a heat lamp focused directly on the animal suggests a simple and practical method for control of PAS in the recovery room, without employing pharmacologic agents,[24,25,**] which may have deleterious side effects. By overriding the response to cold stimulus it would be possible to prevent the metabolic changes in PAS. Since thermal discomfort is closely linked with shivering in humans, such treatment could have an additional positive effect on the postoperative experience of the patient.

** Claybon LE, Hirsh RA: Meperidine arrests postanesthesia shivering (abstract). ANESTHESIOLOGY 53:S180, 1980.

References

1. Roe CF, Goldberg MJ, Blair CS, Kinney, JM: The influence of body temperature on early postoperative oxygen consumption. Surgery 60:85–92, 1966
2. Moir DD, Doyle PM: Halothane and postoperative shivering. Anesth Analg 42:423–428, 1963
3. Jones HD, McLaren CAB: Postoperative shivering and hypoxaemia after halothane, nitrous oxide and oxygen anaesthesia. Br J Anaesth 37:35–41, 1965
4. Rosenberg H, Clofine R, Bialik O: Neurologic changes during awakening from anesthesia. ANESTHESIOLOGY 54:125–130, 1981
5. Pflug AE, Aasheim GM, Foster C, Martin RW: Prevention of post anesthesia shivering. Can Anaesth Soc J 25:43–49, 1978
6. Tammisto T, Tigerstedt I: Restlessness and shivering after naloxone reversal of fentanyl-supplemented anaesthesia. Acta Anaesthesiol Scand 23:51–56, 1979
7. Vaughan MS, Vaughan RW, Cork RC: Postoperative hypothermia in adults: Relationship of age, anesthesia, and shivering to rewarming. Anesth Analg 60:746–751, 1981
8. Emmers R, Akert K: A Stereotaxic Atlas of the Brain of the Squirrel Monkey. Madison, University of Wisconsin Press, 1963
9. Stitt JT, Hardy JD: Thermoregulation in the squirrel monkey (Saimiri sciureus). J Appl Physiol 31:48–54, 1971
10. Hemingway A: Shivering. Physiol Rev 43:397–422, 1963
11. Stuart D, Ott K, Iskikawa K, Eldred E: The rhythm of shivering: II. Passive proprioceptive contributions. Am J Phys Med 45: 75–102, 1966
12. Gonzalez ER: Stopping postop shivers eases rewarming. JAMA 248:2802, 1982
13. Bay J, Nunn JF, Prys-Roberts C: Factors influencing arterial PO during recovery from anaesthesia. Br J Anaesth 40:358, 1968
14. Horvath SM, Spurr GB, Hutt BK, Hamilton LH: The metabolic cost of shivering. J Appl Physiol 8:595–602, 1956
15. Lipton JM, Dinarello CA, Kennedy JI: Fever produced in the squirrel monkey by human leukocytic pyrogen. Proc Soc Exp Biol Med 160:426–428, 1979
16. Murphy MT, Richards DB, Lipton JM: Antipyretic potency of centrally administered α-melanocyte stimulating hormone. Science 221:192–193, 1983
17. Lipton JM, Glyn JR, Zimmer JA: ACTH and melanotropin in central temperature control. Fed Proc 40:2760–2764, 1981
18. Bourke DL, Wurm H, Rosenberg M, Russell J: Intraoperative heat conservation using a reflective blanket. ANESTHESIOLOGY 60:151–154, 1984
19. Holdcroft A, Hall GM, Cooper GM: Redistribution of body heat during anaesthesia. Anaesthesia 34:758–764, 1979
20. Harris WS, Lipton JM: Intracerebroventricular taurine in rabbits: Effects on normal body temperature, endotoxin fever and hyperthermia produced by PGE_1 and amphetamine. J Physiol (Lond) 266:397–410, 1977
21. Clark SM, Lipton, JM: Hypothermia produced in aged squirrel monkeys by central administration of taurine. Exp Aging Res 7:17–24, 1981
22. Cabanac M, Duclaux R, Chatonnet J: Influence d'une élévation passive de la température interne sur les comportement thermorégulateur du chien. J Physiol (Paris) 58:214, 1966
23. Penrod KE: Oxygen consumption and cooling rates in immersion hypothermia in the dog. Am J Physiol 157:436–444, 1949
24. Brichard G, Johnstone M: The effect of methyl-phenidate (Ritalin) on post-halothane muscular spasticity. Br J Anaesth 42:718–721, 1970
25. Pauca AL, Savage RT, Simpson S, Roy RC: Effect of pethidine, fentanyl and morphine on post-operative shivering in man. Acta Anaesthesiol Scand 28:138–143, 1984