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Perioperative Shivering

Physiology and Pharmacology

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IN homeothermic species, a thermoregulatory system coordinates defenses against cold and heat to maintain internal body temperature within a narrow range, thus optimizing normal physiologic and metabolic function. The combination of anesthetic-induced thermoregulatory impairment and exposure to a cool environment makes most unwarmed surgical patients hypothermic.[1–7] Although shivering is but one consequence of perioperative hypothermia, and rarely the most serious, it occurs frequently (*i.e.*, 40–60% after volatile anesthetics),[8,9] and it remains poorly understood. While cold-induced thermoregulatory shivering remains an obvious etiology, the phenomenon has also been attributed to numerous other causes.

Our first goal is to review the organization of the thermoregulatory system, and particularly the physiology of postanesthetic shivering. We then discuss the pharmacology of thermoregulation and review the putative mechanisms and sites of action of various antishivering drugs.

Neuronal Networks Controlling Thermoregulation

Historically, the lateral spinothalamic tract was considered the sole thermoafferent pathway, projecting to the hypothalamic thermoregulatory centers.[10] However, evidence suggests that the majority of these ascending pathways terminate in the reticular formation[11,12] and that thermosensitive neurons exist at several regions outside the preoptic-anterior hypothalamus, including the ventromedial hypothalamus,[13] the midbrain,[14–17] the medulla oblongata,[18,19] and the spinal cord.[20,21] Multiple inputs from various thermosensitive sites are integrated at numerous levels within the spinal cord and brain to provide a coordinated pattern of defense responses.[22,23]

The temperature-regulating system of mammals is often divided into three components: thermosensors and afferent neural pathways, integration of thermal inputs, and effector pathways for autonomic and behavioral regulation. The major afferent thermoregulatory structures and the efferent shivering pathway are depicted in figure 1.

Thermosensors and Afferent Neural Pathways

Spinal Cord. The thermosensitivity of the spinal cord and its thermoregulatory significance is beyond doubt[24–29] and has been reviewed comprehensively.[20] Its ability to sense and modulate thermal signals was pivotal for development of the currently accepted multiple-input, multilevel concept of thermoregulation.[22] In fact, all thermoregulatory effector mechanisms are modulated by spinal cord temperature. In intact[30] and chronically spinalized[31] dogs and rabbits,[32] selective cooling of the spinal cord induces cold tremor. In humans, shivering is rare and of low intensity below the level of injury in patients with spinal cord transection.[33]

The Extrahypothalamic Brain Stem. Thermosensitive sites that are not associated with defined anatomic structures appear to be dispersed in the lower brain stem.[34] Experiments in rats suggest that heat gain responses are powerfully regulated by a tonic inhibitory mechanism located in the midbrain and upper pons.[35] In the reticular formation‡ of the rat, two anatomically separate groups of neurons are involved in thermal responsiveness and control of thermoregulatory muscle tone and shivering.[14] A comparative study in vertebrates also concluded that peripheral thermal input to the hypothalamic areas is *via* the polysynaptic nonspecific reticular areas in the brainstem.[12]

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‡The reticular formation is an area that occupies the central core of the brain stem and refers to the fact that the dendrites of the cells in this area are arranged in bundles that together form a net-like pattern. The reticular formation can be divided in three zones: (1) a median and paramedian zone, which consists of the raphe nuclei; (2) a medial zone, which contains many large cells, also subdivided in a number of centers, *e.g.* the nucleus reticularis gigantocellularis and the (sub-) cuneiform nuclei; and (3) the lateral, parvicellular zone.

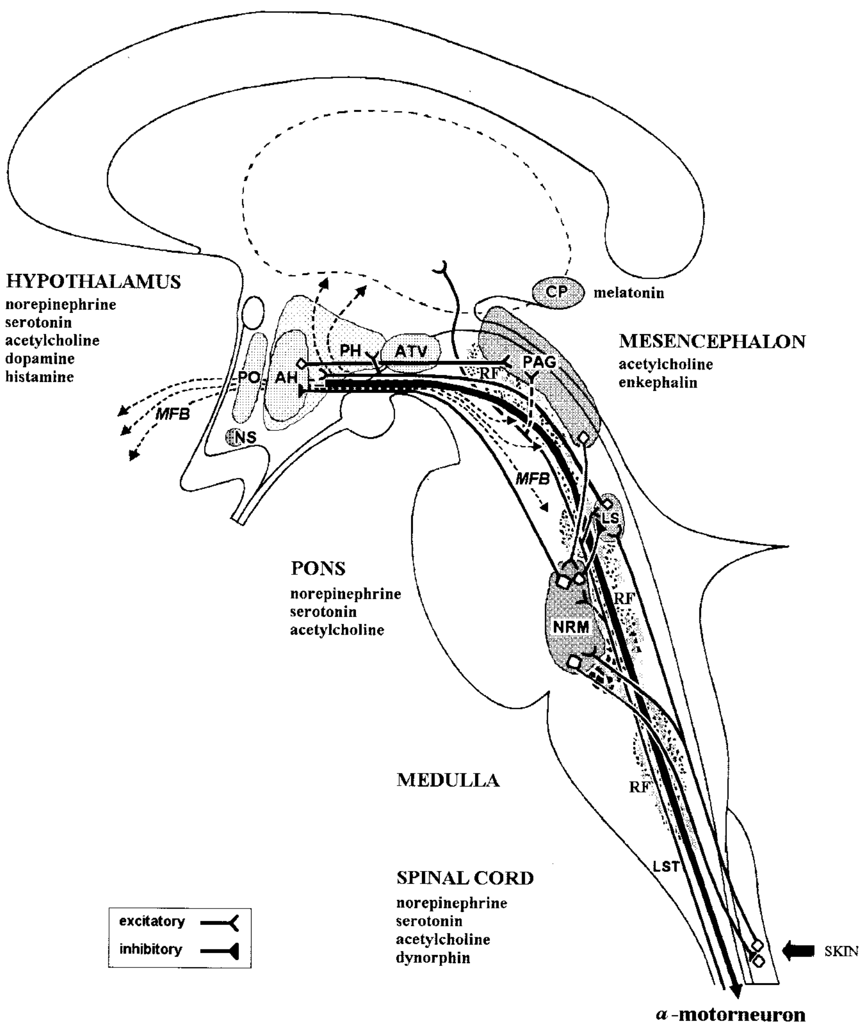

Fig. 1. Neural pathways in the control of shivering. The lateral spinothalamic tract projects to hypothalamic thermoregulatory centers and to nuclei in the pons and mesencephalon. The nucleus raphe magnus plays an important role in transmitting thermal information to the hypothalamus and has an inhibitory role in shivering. Another important relay station is the locus subcoeruleus, which has a predominantly opposite response to cold exposure compared with the nucleus raphe magnus. Importantly, the preoptic area and the most rostral anterior hypothalamus have thermosensitivity. Although shivering can be independently controlled by cold-sensitive spinal neurons in some species, supraspinal facilitation is necessary in humans. The efferent shivering pathway starts at an area between the anterior and the posterior hypothalamus, or at the posterior hypothalamus, and makes multiple connections with the reticular formation in the mesencephalon, pons, and medulla before it ends at the α motor neurons. See text for a detailed explanation of the connecting pathways and neurochemical systems. CP = corpus pineale; MFB = medial forebrain bundle; NS = nucleus suprachiasmaticus; PO = preoptic area; AH = anterior hypothalamus; PH = posterior hypothalamus; ATV = area tegmentalis ventralis; PAG = periaqueductal gray; LS = locus subcoeruleus–coeruleus complex; NRM = nucleus raphe magnus; LST = lateral spinothalamic tract; RF = reticular formation. The basic scheme of the diagram is modified from Nieuwenhuys.[351]

The Nucleus Raphe Magnus and the Subcoeruleus Area. The nucleus raphe magnus in the medulla contains a relatively high percentage of serotonergic thermoresponsive neurons, with a preponderance of warm responsive neurons.[18] The locus subcoeruleus is a circumscribed area in the pons ventromedially to the locus coeruleus,[36] which contains the largest cluster of noradrenergic neurons in the brain.[37] The nucleus raphe magnus and the subcoeruleus area appear to be important relay stations in the transmission of thermal information from skin to hypothalamus.[36,38] These areas seem to be responsible for the modulation rather than the generation of thermal afferent information.[39–41]

Integration of Thermal Inputs

Most investigators accept that the preoptic region of the anterior hypothalamus is the dominant autonomic thermoregulatory controller in mammals. However, preoptic-anterior hypothalamus neurons also respond to nonthermal information, *e.g.*, reproductive hormones,[42] plasma osmolality,[43–45] glucose concentration,[43,46] blood pressure,[47] noxious stimuli,[48] carbon dioxide,[49] and emotional stimuli.[50] Much of the excitatory input to warm-sensitive neurons in the preoptic-anterior hypothalamus comes from the hippocampus,[51] which links the limbic system (emotion, memory, and behavior) to thermoregulatory responses.

In addition, the level of activity in preoptic neurons is modulated by arousal state[52] and suprachiasmatic nucleus activity,[53] which may explain why changes in body temperature are associated with sleep and circadian rhythms. Thus, warm-sensitive neurons in the preoptic-anterior hypothalamus not only sense core temperature but also compare local information with thermal and nonthermal synaptic afferents arriving over ascending pathways. These interactions are inevitable because the thermoregulatory system has few specific effector organs and must be understood as a part of the adaptive responses of the organism as a whole.[54]

Classic neuronal models of the hypothalamus functionally separate the integrative and effector neurons controlling thermoregulatory responses.[55] However, electrophysiologic studies suggest that some anterior hypothalamic neurons act as sensors as well as integrators[56] and suggest a link between neuronal firing rate and the range of thermosensitivity.[57] The model of Bou-

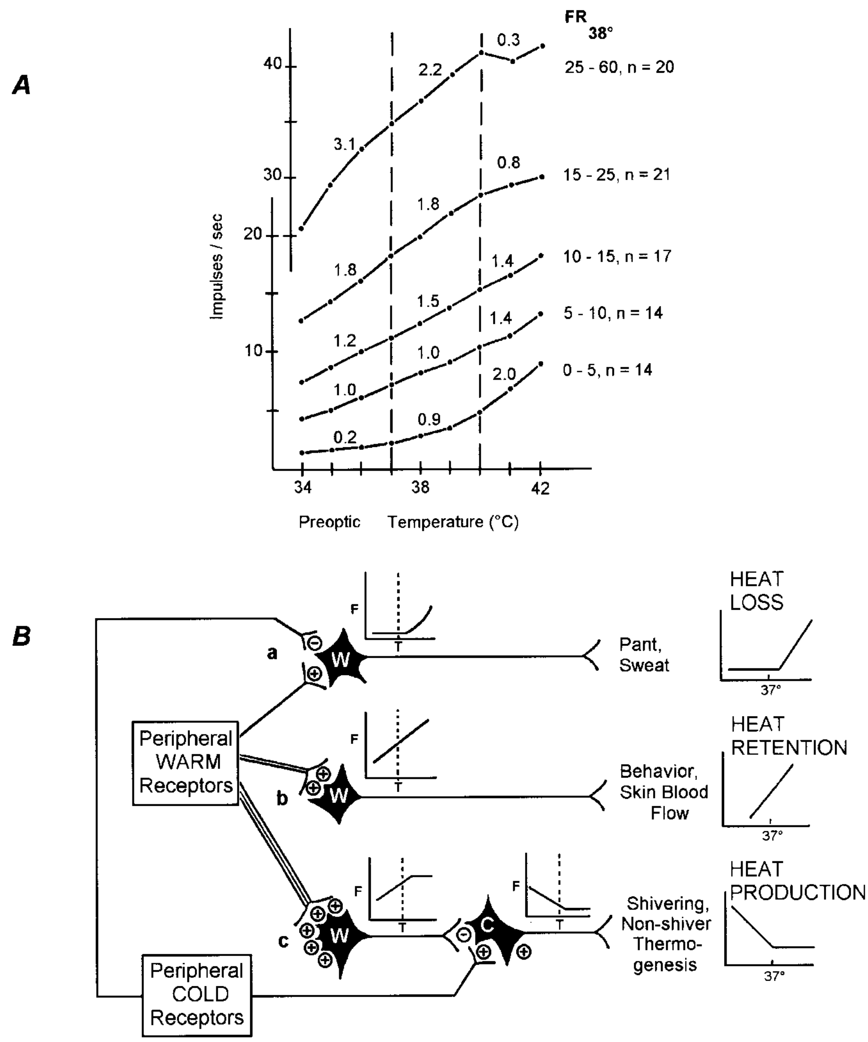

Fig. 2. Relation between neuronal firing rate and range of thermosensitivity. (*A*) Average thermoresponse curves of 86 warm-sensitive neurons recorded in rabbit preoptic-anterior hypothalamus. Neurons were placed into five groups based on their spontaneous firing rates at 38°C (FR 38), *i.e.*, the average core temperature in an anesthetized rabbit. Values above each section indicate the slopes over each temperature range. (*B*) Neuronal model showing hypothesized thermoregulatory roles for warm-sensitive neurons (W) and cold-sensitive neurons (C), based on each neuron's range of thermosensitivity. (+) = excitatory input; (−) = inhibitory input; F = firing rate; T = preoptic temperature; dashed line = thermoneutral preoptic temperature. The warm-sensitive neurons with the lowest firing rates express their thermosensitivity in the hyperthermic range and therefore control heat loss responses. In contrast, warm-sensitive neurons that have medium firing rates apparently control heat-retention responses (skin blood flow, behavior). Finally, warm-sensitive neurons with the highest firing rates decrease their firing rates during hypothalamic cooling, and thus control heat production responses such as shivering and nonshivering thermogenesis. Data are from Boulant.[57]

lant[57] identifies different groups of warm-sensitive neurons, distinguished by their spontaneous firing rates. Varying combinations of afferent inputs trigger different groups of warm-sensitive neurons, and effector mechanisms are therefore activated in an orderly fashion (fig. 2).

Effector Pathways

All neuronal models of temperature regulation use the concept of the common central command: multiple inputs are integrated into a common efferent signal to the effector systems.[58] In both animals[59] and humans,[60] effector mechanisms are called on in an orderly fashion, ensuring optimal regulation at minimum cost. The principal defenses against hypothermia in humans include skin vasomotor activity, nonshivering thermogenesis, shivering, and sweating.

Heat loss is normally regulated without the major responses of sweating or shivering because cutaneous vasodilation and vasoconstriction usually suffice.[56,61] Thermoregulatory vasoconstriction[62] decreases cutaneous heat loss[63,64] and constrains metabolic heat to the core thermal compartment.[65,66] This usually prevents body temperature from decreasing the required additional 1°C required to activate intraoperative shivering.[67–70] Normal thermoregulatory shivering is thus a last-resort defense that is activated only when behavioral compensations and maximal arteriovenous shunt vasoconstriction are insufficient to maintain core temperature.

Nonshivering thermogenesis is the result of cellular metabolic processes that do not produce mechanical work. Thermoregulatory nonshivering thermogenesis has been demonstrated in the human neonate[71] and in rodents, but its existence in adult humans is uncertain,[72] as it is not observed in anesthetized adults[73] or infants.[74]

Shivering

Shivering is an involuntary, oscillatory muscular activity that augments metabolic heat production. Vigorous shivering increases metabolic heat production up to 600% above basal level.[75] However, a doubling of metabolic heat production is all that can be sustained over

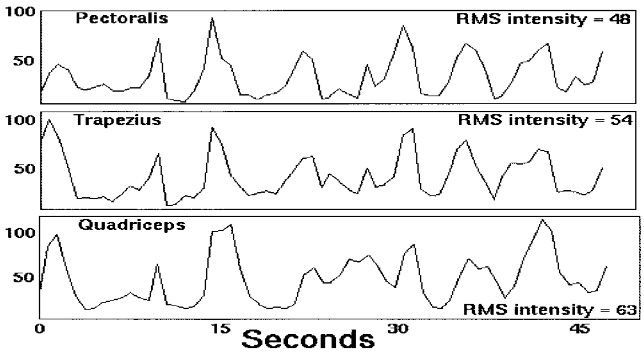

Fig. 3. Normal shivering is characterized by a 4–8 cycle/min "waxing-and-waning" pattern. Shivering intensity varies synchronously in widely distributed muscles, suggesting a central controller. Data are from Sessler *et al*.[78]

long periods.[76] The fundamental tremor frequency on the electromyogram in humans is typically near 200 Hz. This basal frequency is modulated by a slow, 4–8 cycles/min, waxing-and-waning pattern (fig. 3).[77,78]

Shivering is elicited when the preoptic region of the hypothalamus is cooled.[79] Efferent signals mediating shivering descend in the medial forebrain bundle.[80] Classically, a central descending shivering pathway was thought to arise from the posterior hypothalamus.[81–85] Although the preoptic-anterior hypothalamus is thought to suppress shivering by inhibition of the posterior hypothalamus,[86] experimental evidence is lacking. Thermally induced changes in neuronal activity in the mesencephalic reticular formation[87] and the dorsolateral pontine and medullary reticular formation[14] exert descending influences on the spinal cord that increase muscle tone.[14] It remains to be determined whether the reticulospinal neurons receive synaptic input directly from the preoptic-anterior hypothalamus or from the posterior hypothalamus.

Spinal α motor neurons and their axons are the final common path for both coordinated movement and shivering.[88] A typical cold tremor has a specific rhythm in the form of grouped discharges in the electromyography.[89–91] One hypothesis suggests that excitability of motor neurons is inversely proportional to cell size.[92,93] During continued cold stimulation of the skin or the spinal cord, motor neurons are recruited in sequence of increasing size, starting with the small γ motor neurons that are followed by the small tonic α motor neurons, and finally, the larger phasic α motor neurons.[92,94,95]

The larger α motor neurons are more likely to manifest synchronized discharges than smaller ones.[96] Synchronization of motor neurons during shivering may be mediated by recurrent inhibition through Renshaw cells, a group of inhibitory interneurons identified in the cat.[97,98] Reflex activation of α motor neurons *via* the γ muscle spindle loop (instability of the stretch reflex feedback system), is another potential but controversial mechanism that could determine the rhythm and frequency of α motor neurons discharges.[99–101]

Postanesthetic Shivering and Shivering-like Tremor

Postanesthetic Shivering

Patients report that shivering is remarkably uncomfortable, and some even find the accompanying cold sensation worse than surgical pain. Moreover, shivering *per se* may aggravate postoperative pain simply by stretching surgical incisions. Shivering also occasionally impedes monitoring techniques,[102,103] increases intraocular[104] and intracranial[105] pressures, and is especially disturbing to mothers during labor and delivery.[106]

Shivering can double or even triple oxygen consumption and carbon dioxide production, although the increases are typically much smaller.[107,108] These large increases in metabolic requirement might predispose to difficulties patients with existing intrapulmonary shunts, fixed cardiac output, or limited respiratory reserve. However, shivering is rare in elderly patients[109–111] because age *per se* impairs normal thermoregulatory control.[112–117] Because shivering intensity is markedly reduced in elderly and frail patients, it is unlikely that shivering itself provokes serious adverse outcomes in these patients.

Likewise, shivering is rarely associated with clinically important hypoxemia because hypoxia itself inhibits this response.[118,119] Morbid cardiac outcomes associated with mild perioperative hypothermia appear to be mediated by a mechanism more subtle than shivering—perhaps the associated marked increase in plasma catecholamine concentrations.[120]

Abnormal Tremor Patterns

Shivering is common in hypothermic patients recovering from general anesthesia.[121–123] The conventional explanation for postanesthetic tremor is that anesthetic-induced thermoregulatory inhibition abruptly dissipates, thus increasing the shivering threshold toward normal. Discrepancy between the persistent low body temperature and the now, near-normal, threshold activates simple thermoregulatory shivering. Difficulties with this proposed explanation include the observations that tremor frequently is *not* observed in markedly hypothermic patients[122] and that tremor occurs commonly in normothermic patients.[124] However, a subsequent study[78] suggested that special factors related to surgery (such as stress or pain) might contribute to the genesis of postoperative tremor because it failed to identify any shivering-like activity in normothermic volunteers. Pain might facilitate shivering-like tremor in both postoperative patients[125] and in women having spontaneous term labor.[126]

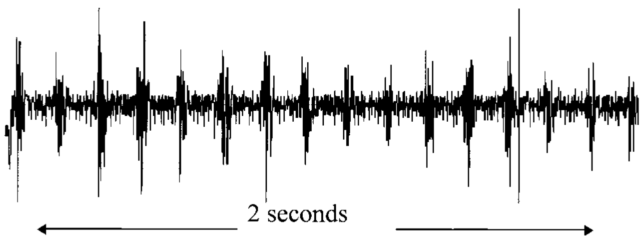

Fig. 4. A clonic tremor can be observed at low end-tidal concentrations of the volatile anesthetics (*i.e.*, 0.2–0.4% isoflurane). This tremor has a 5–7 Hz "bursting" electromyographic pattern that is identical to that produced by clonus after spinal cord transection. It is often accompanied by other spinal reflexes, including nystagmus and exaggerated deep-tendon responses. Data are from Sessler *et al*.[78]

Any increase in the thermoregulatory set-point (fever) may be associated with normal thermoregulatory shivering in normothermic or even hyperthermic patients.[124,127] Surgical stress may increase the thermoregulatory set-point in the postoperative period: even in the absence of clinically evident signs of infection, 25% of postoperative patients reach core temperatures of 38°C, and 50% of them reach 38.4°C.[128] Of course, there are many other reasons surgical patients might develop a fever, including infection, atelectasis, and release of pyrogenic substances by injured tissues.

Three patterns of muscular activity were observed in hypothermic volunteers during emergence from isoflurane anesthesia.[78] The first was a tonic stiffening and appeared to be largely a direct, non–temperature-dependent effect of isoflurane anesthesia. Near 0.3% end-tidal isoflurane concentration, a second pattern was overt: synchronous, tonic waxing and waning. This was by far the most common pattern and resembled that produced by cold-induced shivering in unanesthetized volunteers, or "true" thermoregulatory shivering.[77] The third observed pattern was a spontaneous electromyographic clonus that required both hypothermia and residual isoflurane end-tidal concentrations between 0.4 and 0.2% (fig. 4). During epidural anesthesia, synchronous waxing-and-waning patterns were present; however, no abnormal (*i.e.*, clonic) electromyogram patterns were detected.[129]

Despite alternative etiologies in some patients, normal thermoregulatory shivering in response to core and skin hypothermia remains by far the most common cause of postoperative shivering. The remainder of this review therefore focuses on normal thermoregulatory shivering.

Dependence of Thermosensitivity on the State of Arousal

Although it is not possible to focus a thermal stimulus to a single cell, there are thermosensitive units in the hypothalamus that might be considered thermoresponsive.[130] These units may be activated by direct thermal stimulation or by other interconnected interneurons responding to thermal stimulation of the skin or distant areas in the central nervous system. Thermoresponsiveness of these units is not constant but varies significantly over time[52,131] and depends on the state of vigilance[52,132] and cortical activity.[133–135]

Recent work demonstrated the potential for arousal state to combine with thermal influences to create the appearance that cells are thermosensitive or thermoresponsive when, in fact, they may not be responding directly to temperature. Thus, when electroencephalographic state changes are taken into account, all changes in firing rate of preoptic-anterior hypothalamic cells that appeared to be responsive to changes in skin temperature are associated with electroencephalographic state changes.[136] Single-unit responses in the rostral ventromedial medulla, which consists of the nucleus raphe magnus and adjacent brain stem regions, are not specific for temperature manipulations but reflect changes in electroencephalogram–electromyogram activity, which in turn is determined by a variety of factors, including thermal and noxious stimuli.[137] Similar results (no thermoresponses observed within a given electroencephalographic state) were obtained for single-unit activity in the subcoeruleus area.[138]

Pharmacologic Modulation of Shivering

Several classes of substances, including biogenic monoamines, cholinomimetics, cations, endogenous peptides, and possibly *N*-methyl-D-aspartate (NMDA) receptor antagonists, appear to modulate central thermoregulatory control mechanisms. In this section, we discuss these chemically induced changes in thermosensitivity and modulation of thermosensitivity by drugs used to control postanesthetic shivering. The predominant site of action of the discussed drugs is in most, if not all, instances difficult to establish.

Potent antishivering properties have been attributed to numerous drugs.[105,139–154] The normal functions of these drugs are diverse. Not discussed further in this review is the use of neuromuscular blocking agents to suppress shivering in hypothermic patients who are mechanically ventilated.[155,156]

Biogenic Amines

Pharmacologic Evidence. The Monoamine Theory of thermoregulation was born with Feldberg and Myers' suggestion in 1963 that the balance of norepinephrine and serotonin (5 hydroxytryptamine [5-HT]) in the preoptic-anterior hypothalamus controls the body temperature set-point.[157] Initially, specific thermoregulatory responses were demonstrated in the cat by direct intracerebroventricular injection of adrenergic and serotonergic neurotransmitters. The monoamines seemed to have opposite effects: 5-HT caused shivering and vasoconstriction and a concomitant increase in core temperature, whereas norepinephrine and epinephrine lowered the normal resting temperature of the cat and attenuated the 5-HT-induced hyperthermia.[158]

In similar experiments, other species reacted in the opposite way, *i.e.*, norepinephrine increased and 5-HT decreased body temperature. These interspecies differences have been reviewed in detail by other investigators.[159–161] Contradictory results were reported for monoamines in a given species as well, and were attributed to differences in dosage,[162] microinjection technique,[163] ambient temperature,[164,165] and other factors.[166]

Neurotransmitters modulate the synaptic input on temperature-sensitive neurons and may have profound effects on their firing rates and range of thermosensitivity. The way thermal signals from cold and warm sensors are integrated in the hypothalamus led to speculation that the set-point of the thermoregulatory system could be easily manipulated if the few specific inputs consisted of certain transmitters.[167] This turned out to be a considerable oversimplification because thermoregulatory thresholds are determined by multiple modulatory thermal and nonthermal inputs (that are not all monoaminergic) and take place at all levels of hierarchy in the thermoregulatory system. Nevertheless, the balance between the modulatory 5-HT and norepinephrine inputs may be responsible for short- and long-term thermoregulatory adaptive modifications of the shivering threshold.[39,55,168]

Norepinephrine microdialyzed into the preoptic area of conscious guinea pigs reduces core temperature, a reduction that is abolished by coadministration of the α_2-adrenoceptor antagonists yohimbine and rauwolscine.[169] The α_2-adrenoceptor agonist clonidine evokes dose-dependent reductions in core temperature, whereas α_1-, β_1-, and β_2-adrenoceptor agonists and antagonists do not induce significant changes in core temperature. Elevation of the ambient temperature to 40°C induces a selective increase in the release of norepinephrine perfusates collected with a push-pull cannula from the rostral hypothalamus of the cat,[170] whereas decreasing the ambient temperature to 2°C markedly reduces the norepinephrine release from the preoptic-anterior hypothalamic area of the rat.[171]

5-Hydroxytryptamine may influence both heat production and heat loss pathways. Apart from interspecies differences, 5-HT elicits divergent thermoregulatory responses at different thermosensitive sites within the hypothalamus. Injection of 5-HT into the preoptic area of cats evokes hypothermia accompanied by vasodilation.[172] When 5-HT is injected into the rostral hypothalamus of cats, hyperthermia associated with shivering is evoked.[172] In rat midbrain slice preparations, the majority of warm-sensitive units and all cold-sensitive units are inhibited by 5-HT.[173] In contrast, 5-HT activates the majority of temperature-sensitive units in the medulla oblongata of the rat.[173]

Opposite modulatory inputs from noradrenergic and serotonergic neurons in the lower brain stem modify the composite skin temperature signal integrated at the level of the hypothalamus, thereby shifting the thresholds and slopes for thermoregulatory responses.[168] In different physiologic situations, *e.g.*, during cold adaptation or during fever, the interthreshold range (temperatures between the sweating and shivering thresholds) widens or

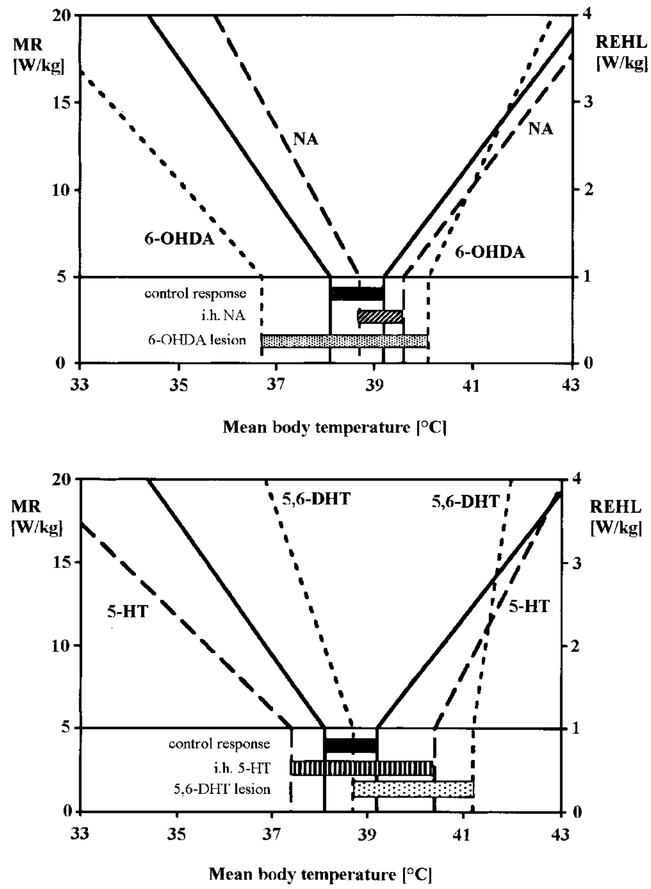

Fig. 5. Antagonistic brain stem modulatory inputs change the threshold and gain of thermoregulatory responses in guinea pigs. The horizontal line at the metabolic rate (MR) of 5 W/kg denotes the normal value measured at thermoneutral ambient temperature. Intrahypothalamic (i.h.) microinjection of noradrenaline (NA) shifts the threshold temperatures for the onset of cold defense to higher temperatures. Microinjection of serotonin (5-HT) into the hypothalamus shifts the shivering threshold to lower temperatures. Selective lesions of noradrenergic or serotonergic input, respectively, by the neurotoxins 6-hydroxydopamine (6-OHDA) and 5,6 dihydroxytryptamine (5,6-DHT) are denoted by the dotted lines. Both NA and 5-HT microinjections increase the threshold temperatures for heat defense (increase in respiratory evaporative heat loss [REHL]), and these changes could not be reversed by selective neurochemical lesions. Intrahypothalamic microinjections release prostaglandins, which increase threshold temperatures for heat defense reactions. The shaded bars indicate the width of the interthreshold zone (ITZ), which depends on the balance between the modulatory NA and 5-HT inputs. For example, a wide ITZ results when 5-HT input dominates in cold-adapted guinea pigs. Data are from Zeisberger.[168]

narrows. In cold-adapted guinea pigs, for example, serotonergic input dominates and produces a wide interthreshold zone with an average body temperature of 38°C (compared with 39°C when the norepinephrine input dominates).[174] Similarly, the interthreshold zone nearly doubles in cold-adapted humans, mainly because the shivering threshold is reduced by approximately 1°C to 35.4°C.[175] Despite multiple confounding factors, there is increasing evidence for the involvement of monoaminergic brain systems in adaptive changes in thermoregulation (fig. 5).[55,161]

Dopamine injected into the hypothalamus of the unanesthetized monkey in the same range of doses as norepinephrine induced hypothermia, but to a lesser degree.[176] In single-unit studies, the spontaneous firing rate of cold-sensitive neurons of the cat's hypothalamus decreased when dopamine was applied iontophoretically.[177] Perfusion with dopamine increased the firing rate of many warm-sensitive neurons in hypothalamic slices.[178] In a hot environment, dopamine was increased in push-pull perfusates within the preoptic-anterior hypothalamic area of the cat.[179] During cold exposure, shivering thermogenesis is inhibited after intracerebroventricular injection of dopamine in the goat.[180] Furthermore, dopamine in the nigrostriatal system may play a role in central thermoregulation.[181]

Histaminergic pathways also may be involved in central thermoregulation, *via* both H_1 and H_2 histamine receptors, as demonstrated in behavioral studies.[182–184] There is some evidence for histaminergic pathways in the rostral hypothalamus involved in thermoregulation and integration with other monoaminergic thermoregulatory pathways, as reviewed previously.[185]

Drug Effects. Nefopam,[186] an analgesic with powerful antishivering properties,[105] is a potent inhibitor of synaptosomal uptake of 5-HT, norepinephrine, and dopamine,[187] and slightly lowers normal body temperature.[188] Tramadol[189,190] is an antishivering drug[146] with a similar mechanism of action: it inhibits the reuptake of 5-HT,[191] norepinephrine,[192] and dopamine[193] and facilitates 5-HT release.[191] Despite different degrees of opioid-like characteristics in preclinical tests,[192] tramadol lacks significant naloxone reversibility in humans.[194,195] In human volunteers, a high dose of naloxone only partially reverses the antishivering effect of tramadol.[146] Cerebral α_2 adrenoceptors are thought to play a role in the attenuation of postoperative shivering by tramadol.[196]

α_2-Adrenergic agonists[197] hyperpolarize neurons, presumably by increasing potassium conductance through G_i-coupled proteins.[198,199] This, in turn, suppresses neuronal firing,[200] which is linked to the range of thermosensitivity.[57] Furthermore, activation of α_2-adrenoceptors suppresses N-type calcium entry into nerve cells,[200] which depresses neurotransmitter release.[201] A greater retention of Ca^{2+} ions on the neuron's surface stabilizes the cell membrane and lowers the firing rate of heat gain units in the posterior hypothalamus.[202]

The antihypertensive drug ketanserin also interferes with postanesthetic shivering; however, the efficacy of ketanserin is rather low.[141,203] Ketanserin is an antagonist with high affinity for both 5-HT_2 receptors[204 205,206] and α_1 adrenoceptors.[207,208] Similar to other α_1-adrenoceptor antagonists (*e.g.*, prazosin), ketanserin acts indirectly *via* facilitation of a central presynaptic α_2-adrenoceptor mechanism in the lower brainstem.[208]

5-Hydroxytryptamine type 3 receptor antagonists, known as antiemetic drugs, are currently under investigation for a possible role in the prevention and treatment of postanesthetic shivering.[154,209] There are almost no animal data available about 5-HT_3 receptor–mediated temperature-regulating mechanisms.[210]

Sites of Action. The effects of nefopam[187] and tramadol[191,192] at the level of the pons may partially explain their antishivering effect. In the rat locus coeruleus, tramadol and its main metabolite, O-desmethyltramadol, reduce neuronal firing rate and hyperpolarize neurons in a concentration-dependent manner.[211] The locus coeruleus appears to be a proshivering center that activates heat production in rodents.[55] The locus coeruleus is also the main noradrenergic nucleus involved in the descending pain-control system,[212] with its activity regulated by α_2 autoreceptors.§ 5-HT_{1A} receptors modulate responses mediated by α_{2A} adrenoceptors in the locus coeruleus.[213] In humans, α_2-adrenoceptor antagonism with yohimbine significantly reverses the analgesic effects of tramadol.[195]

Racemic tramadol and its (+) enantiomer significantly reduce 5-HT uptake and increase stimulated 5-HT efflux in the dorsal raphe nucleus.[214] The dorsal raphe nucleus is part of the brainstem raphe complex and is considered one of the most important nuclei in the modulation of pain in the central nervous system.[212] The nucleus raphe magnus is an antishivering center that activates heat loss mechanisms and inhibits thermogenesis during cold adaptation.[55,215] 5-HT is the major neurotransmitter in the raphe nuclei, but half of the raphe cells that project to the spinal cord are not serotoninergic.[216] There is also a significant amount of norepinephrine in the nucleus raphe magnus, and approximately 10% of nucleus raphe magnus serotoninergic cells express α_2 adrenoreceptors.[217]

An inhibitory role of the nucleus raphe magnus on shivering is caused by projections to hypothalamic units and by a second pathway descending from the nucleus raphe magnus to the spinal cord where dorsal horn cells are inhibited presynaptically.[40] Postsynaptic activation of noradrenergic units in the subcoeruleus region inhibit

§Autoreceptors are presynaptic receptors that respond to the transmitters released by the same nerve ending on which the receptors are located. They are usually inhibitory. The best-known autoreceptors are the presynaptic α_2-receptors that are activated by norepinephrine or clonidine.

warm-responsive units in an area between the anterior hypothalamus and the posterior hypothalamus, and in the posterior hypothalamus itself.[38] Other projections of the subcoeruleus region descend to the pons and medulla and to motor neurons and autonomic preganglionic cell groups in the spinal cord.[218] Just as descending inhibition restricts transmission of pain signals, efferents to the dorsal horn of the spinal cord may inhibit cutaneous thermal input.[215,219,220] However, this assumption remains controversial.[221] In the very least, descending 5-HT terminals from the locus coeruleus make intimate contact with motor neurons, mostly *via* cord internuntials.[222–224] However, the role of these nerve terminals in the modulation of shivering remains to be established.

An anatomic target for the antishivering effect of α_2-adrenergic agonists can be found at three levels. First, a small intravenous dose of clonidine reduces the spontaneous firing rate in the locus coeruleus[225] and indirectly reduces norepinephrine-induced firing of serotoninergic neurons in the dorsal raphe nucleus.[226] Second, the action of α_2-adrenergic agonists in the locus coeruleus may also increase activation of α_2 adrenoceptors in the spinal cord.[227] Intrathecal α_2-adrenergic agonists are known to release dynorphin (a κ-opioid agonist)[228] and to stimulate norepinephrine and acetylcholine release.[229] Dynorphin is present in high concentration in the spinal cord[230] and is involved in antinociception. Norepinephrine and acetylcholine suppress responses of wide-dynamic-range neurons to noxious stimulation in the spinal dorsal horn. As postulated, depressor effects of these neurotransmitters at the dorsal horn may modulate cutaneous thermal input additional to noxious and mechanoreceptive transmission.[215] Third, the hypothalamus contains a high density of α_2 adrenoceptors. Norepinephrine microdialyzed into the hypothalamus, for example, activates α_2 adrenoceptors, reduces metabolic heat production, and produces hypothermia.[169] Pretreatment of the preoptic-anterior hypothalamic area with the selective α_2-adrenoceptor agonist yohimbine inhibited the hypothermic response of clonidine.[231]

Cholinomimetics

Pharmacologic Evidence. In single-unit studies of the preoptic-anterior hypothalamus in cats,[232] rats,[233] and many other species,[161] the effect of acetylcholine on thermosensitive neurons remains inconclusive. The muscarinic or nicotinic cholinoceptors may be involved, because both acetylcholine and nicotine apparently induce vasoconstriction, shivering, and a hyperthermic reaction when injected into the hypothalamus of a conscious monkey.[176,234] Antimuscarinic drugs have been used to demonstrate the physiologic role of the central cholinergic system in thermoregulation. However, a lack of selectivity and other methodologic problems influenced the results: for example, intracerebroventricular administration of atropine in the rabbit suppresses shivering and causes hypothermia,[235] whereas rats become hyperthermic when atropine is injected into the hypothalamus.[236] In rabbits, intravenous injection of nicotine stops shivering.[237]

There is evidence in monkeys that cholinergic activity in the hypothalamus modulates heat gain (shivering) during heat or cold stress. Release of acetylcholine, for example, is markedly increased by 88% at the active acetylcholine-releasing sites within the preoptic-anterior hypothalamic area by peripheral cooling, but suppressed by 80% at the same perfusion sites by peripheral warming.[238] Within the posterior hypothalamus, cold stress doubles acetylcholine release. Injection of a large dose of a cholinomimetic into the posterior hypothalamus causes hypothermia, however, presumably because of a "depolarizing blockade" of the cholinergic receptor system involved in heat production.[161,176]

In the brain stem, cholinoceptors also may participate in thermoregulation, interacting with monoaminergic and peptidergic systems. Microinjection of the cholinoceptor agonists, carbachol and pilocarpine, into the mesencephalic nucleus raphe magnus caused significant hyperthermia, which was blocked by local pretreatment with a muscarinic receptor antagonist as well as a nicotinic receptor antagonist.[239] Intracerebroventricular pretreatment with a 5-HT reuptake blocker significantly inhibited the carbachol-induced hyperthermia, which suggests that the hyperthermia is caused by an inhibition of a 5-HT–sensitive hypothalamic heat loss mechanism. Injection of carbachol into the periaqueductal gray area of rat brain results in hypothermia, probably mediated by neurotensin.[240]

Drug Effects. Physostigmine is as effective in preventing postanesthetic shivering as meperidine and clonidine.[144] Physostigmine is the classic centrally acting cholinesterase inhibitor but is relatively nonselective. The analgesic effect of physostigmine may be mediated *via* cerebral cholinergic muscarinic receptors,[241] but serotoninergic receptors[242] and an endorphinergic mechanism[243,244] may also be involved. Analgesia after intrathecal administration of anticholinesterase is mediated through muscarinic receptors, and there is a synergistic interaction with intrathecal μ-opioid and α_2-adreneric agonists.[245] It is unknown if the same receptors also mediate the thermoregulatory effects of physostigmine.

In a prospective, randomized, double-blind study, healthy adult patients who were premedicated with an anticholinergic had a significantly greater incidence and severity of postoperative shivering than those in a control group.[246] Augmented shivering was evident with both glycopyrrolate and hyoscine, suggesting modulation of a mechanism peripheral to the central nervous system. However, a limitation in this study was that the control group was given metoclopramide, a drug possessing parasympathomimetic activity and that is a selective D_2-dopamine receptor antagonist. Recent data indicate that atropine slightly increases the thresholds triggering vasoconstriction and shivering,[149] which is consistent with the premedication study.

Sites of Action. There are numerous potential anatomic substrates for the antishivering effect of physostigmine, situated at both supraspinal and spinal levels. In addition to the major cholinergic nuclei and pathways, cholinergic interneurons are found throughout the central nervous system.[247] Furthermore, functional interactions between the adrenergic and muscarinic systems are well established.[245,248] Most prominently, there are serotoninergic afferents from the raphe nuclei that project to cholinergic brain stem nuclei.[249] Through dual projections, cholinergic and aminergic brainstem neurons can concurrently modulate the activity of neurons in the thalamus and basal forebrain during cortical arousal.[250] However, the role of these anatomic structures in the thermoregulatory modulation by physostigmine remains hypothetical.

Peptides

Pharmacologic Evidence. A large number of peptides are found in the brain, especially within the hypothalamus, and there is considerable evidence that they participate in central thermoregulatory control.[251] They can be divided into three categories, according to the changes in firing rate of thermosensitive neurons induced by local application of these substances in the preoptic-anterior hypothalamus and the concomitant changes in body temperature.

Local application of thyrotropin-releasing hormone decreases activity of preoptic-anterior warm-sensitive neurons and excites cold-sensitive neurons, thereby producing cold-defense responses and hyperthermia.[252,253] In contrast, hypothermia-producing substances (angiotensin II[254] and morphine[255]) excite and inhibit the activity of preoptic-anterior warm-sensitive and cold-sensitive neurons, respectively. Poikilothermia-producing peptides such as bombesin and neurotensin[256] decrease the firing rate in 50–70% of the preoptic-anterior hypothalamic neurons, regardless of their thermosensitivity, with inhibition of both heat-defense and cold-defense responses. Arginine vasopressin, adrenocorticotropic hormone, and α-melanocyte stimulating hormone are thought to act as endogenous antipyretics during fever.[257,258]

Opioid peptides induce changes in body temperature that depend on the species, dose, ambient temperature, and degree of restraint during testing.[259] Met-enkephalin and β-endorphin induce hyperthermia when given intracerebroventricularly in a low dose, the precise mechanism being unclear.[260] At higher doses, enkephalin and β-endorphin cause hypothermia, probably because of a reduction in metabolic heat production.[261,262] Microinjected into the preoptic-anterior hypothalamus or the periaqueductal gray, β-endorphin evokes hyperthermia,[263,264] as does the injection of enkephalin into the preoptic-anterior hypothalamus.[265] Infusion of β-endorphin into the lateral cerebral ventricle of the rat, however, causes hypothermia.[266]

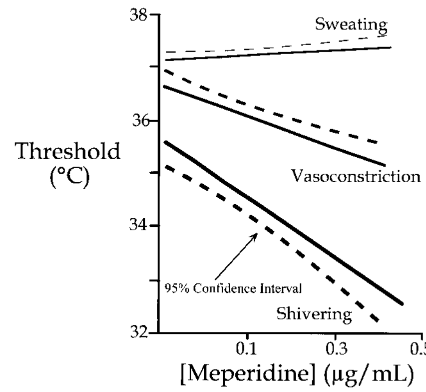

Fig. 6. The sweating threshold increased as a function of plasma meperidine concentration. In contrast, meperidine produced a linear decrease in the core temperature triggering vasoconstriction (slope = $-3.0°C \cdot \mu g^{-1} \cdot ml^{-1}$). Meperidine decreased the shivering threshold nearly twice as much as the vasoconstriction threshold (slope = $-5.6°C \cdot \mu g^{-1} \cdot ml^{-1}$). Dashed lines indicate 95% confidence intervals. These data indicate that meperidine has a special antishivering action that is not shared by other drugs that inhibit thermoregulation—all of which synchronously decrease the vasoconstriction and shivering thresholds. Data are from Kurz *et al*.[279]

Drug Effects. Pure μ-receptor agonists, including morphine (2.5 mg), fentanyl (25 μg), and alfentanil (250 μg), may be significantly better treatments for postanesthetic shivering than placebo.[267–269] Alfentanil is probably effective because increasing plasma concentrations linearly reduce the shivering threshold.[70,270] Epidurally administered sufentanil in patients produces a dose-dependent decrease in shivering response and body temperature.[271] Epidural fentanyl also reduced the shivering threshold when added to lidocaine for epidural anesthesia.[272]

Meperidine[273] is not only an effective treatment for shivering,[274–278] but the drug is clearly more effective than equianalgesic concentrations of pure μ-receptor agonists.[70,276] Meperidine decreases the shivering threshold almost twice as much as the vasoconstriction threshold (fig. 6).[279] This is in distinct contrast to other analgesic and sedative drugs, including propofol,[67] dexmedetomidine,[152] and midazolam[280] (table 1), and to general anesthetics.[68,69] The gain and maximum intensity of shivering remain unchanged during both alfentanil and meperidine administration.[70,279] These results thus demonstrate that the special antishivering effect of meperidine is primarily mediated by a disproportionate reduction in the shivering threshold.

The antishivering action of meperidine may be partially mediated by κ-opioid receptors.[145] Consistent with this theory, nalbuphine and butorphanol, two other antishivering drugs,[140,149,153,281] are known to have κ-opioid receptor activity.[282–284] The difficulty with this the-

Table 1. Concentration Dependence of Thermoregulatory Responses during Administration of Analgesic and Sedative Drugs in Humans

	Shivering Slope	Vasoconstriction Slope	Slope Ratio
Meperidine	$-6.1°C \cdot \mu g^{-1} \cdot ml$	$-3.3°C \cdot \mu g^{-1} \cdot ml$	1.85
Tramadol	$-4.2°C \cdot \mu g^{-1} \cdot ml$	$-3.0°C \cdot \mu g^{-1} \cdot ml$	1.40
Alfentanil	$-0.0057°C \cdot ng^{-1} \cdot ml$	$-0.0049°C \cdot ng^{-1} \cdot ml$	1.16
Nalbuphine	$-2.8°C \cdot ng^{-1} \cdot ml$	$-2.6°C \cdot ng^{-1} \cdot ml$	1.08
Dexmedetomidine	$-2.4°C \cdot ng^{-1} \cdot ml$	$-1.61°C \cdot ng^{-1} \cdot ml$	1.49
Propofol	$-0.7°C \cdot \mu g^{-1} \cdot ml$	$-0.6°C \cdot \mu g^{-1} \cdot ml$	1.17
Midazolam	$-2.0°C \cdot \mu g^{-1} \cdot ml$	$-2.67°C \cdot \mu g^{-1} \cdot ml$	0.75

The shivering-to-vasoconstriction slope ratio of meperidine was the greatest, suggesting a special anti-shivering action. The slope ratios of tramadol and dexmedetomidine, the α_2-agonist, are comparable. Nalbuphine, a κ-opioid receptor agonist, seems to have no special anti-shivering effect. Data are from Kurz,[279] De Witte,[146] Kurz,[70] Greif,[149] Talke,[152] Matsukawa,[67] Kurz.[280]

ory is that recent data indicate that nalbuphine, a mixed μ-antagonist and κ-agonist, comparably reduces the vasoconstriction and shivering threshold in volunteers.[149]

Sites of Action. Possible substrates for the effects of opioids on body temperature and thermoregulatory responses include their actions on preoptic-anterior hypothalamus neurons,[285] dorsal raphe nucleus neurons,[286] raphe magnus neurons,[287] locus coeruleus,[288] and the spinal cord.[272] Generally, opioids exert a variety of stimulatory effects on signal transduction,[289] including stimulation of cyclic adenosine monophosphate formation. Cyclic adenosine monophosphate increases thermosensitivity in warm-sensitive and moderate-slope temperature-insensitive neurons.[290,291]

A significant increase in temperature sensitivity was observed in warm-sensitive preoptic-anterior hypothalamic neurons during administration of the κ-opioid receptor opioid agonist dynorphin A1–17.[285] Selective κ-opioid receptor agonists attenuate the response of locus coeruleus neurons to excitatory inputs; in contrast, the μ-opioid receptor agonist morphine directly inhibits or excites basal locus coeruleus discharge.[292] The extent to which κ-opioid receptors in the hypothalamus, spinal cord,[293] and locus coeruleus contribute to the thermoregulatory effects of meperidine remains unclear. However, the modest thermoregulatory effects of nalbuphine[149] might suggest that mechanisms other than κ-opioid receptor agonism predominate.

Cations

The positive ions calcium (Ca^{2+}) and sodium (Na^{+}) may play a functionally opposing role in mediation of body temperature.[161] In monkeys,[294] perfusion of excess Ca^{2+} into the posterior hypothalamus evokes a decrease in body temperature, whereas perfusion with Na^{+} ions increases body temperature. The magnitude of this response depends on the ratio of the cations' concentration[295] and may thus define the set-point for body temperature. The ratio of these cations in the posterior hypothalamus shifts immediately after an intense peripheral thermal challenge.[202] During conditions of fever and defervescence, push-pull perfusate studies confirm that the ratio of the cations changes corresponding with the direction of change in body temperature.[296,297]

Less experimental data are available on the possible role of magnesium in the regulation of body temperature. Magnesium may be considered a physiologic calcium-channel blocker.[298] Magnesium chloride injected into the third ventricle of the sheep increases body temperature,[299] whereas intracerebroventricular injection of Ca^{2+} elicits hypothermia in other species.[300] During cold exposure, magnesium concentration in rat plasma increases,[301] and in heat-acclimated volunteers, plasma magnesium decreases.[302] In addition, during treatment with magnesium sulfate, a significant decrease in maternal temperature was observed.[303] The possible physiologic role in cold adaptation may thus explain the effectiveness of magnesium in decreasing the threshold of postanesthetic shivering.

N-*methyl-D-aspartate Receptor Antagonists*

Magnesium sulfate is a physiologically occurring competitive antagonist at NMDA receptors[293] and was recently found to stop postanesthetic shivering.[147] Several antishivering drugs share the NMDA receptor antagonist properties of magnesium.

Orphenadrine is both antimuscarinic[304] and has noncompetitive NMDA receptor antagonist properties.[305] Orphenadrine extends the action of perioperative analgesics[306] and thus has been proposed as an alternative to methylphenidate to control postanesthetic shivering.[148]

Ketamine, which is a competitive NMDA receptor antagonist,[307] also inhibits postanesthetic shivering[143]; however, this effect must be interpreted with caution because of the drug's pharmacologic complexity. In addition to being a competitive NMDA receptor antagonist, ketamine has several other pharmacologic properties,[308] including being a κ-opioid agonist,[309] blocking amine uptake in the descending inhibitory monoaminergic pain pathways,[310,311] having a local anesthetic action, and having an interaction with muscarinic receptors.[309]

It is likely that NMDA receptor antagonists modulate thermoregulation at multiple levels. There are neurons in the preoptic-anterior hypothalamus of the rat whose firing rate increases by application of NMDA.[312] Furthermore, NMDA receptors modulate noradrenergic and serotoninergic neurons in the locus coeruleus.[313,314] In the dorsal raphe nucleus, 5-HT acts as a neuromodulator to enhance the effects of NMDA receptors.[286] Finally, the NMDA receptors at the dorsal horn of the spinal cord modulate ascending nociceptive transmission.[293] The relation between nociceptive transmission and afferent thermoregulatory pathways nonetheless remains largely speculative.

Analeptic Agents.

Methylphenidate is effective for prevention and treatment of postanesthetic shivering.[139,315] Methylphenidate is an analeptic agent that binds presynaptic sites on dopamine, norepinephrine, and 5-HT transport complexes, which in turn block reuptake of the respective neurotransmitters.[316,317] Activation of the raphe system and the concomitant arousal[318] may explain the impressive antishivering potency of methylphenidate. However, experimental evidence for the precise anatomic substrate of methylphenidate's antishivering action is lacking.

Doxapram is a low-potency analeptic agent that is best known as a respiratory stimulant. However, it is also an effective treatment for postanesthetic shivering.[142] Although the pharmacology of doxapram remains poorly understood, the drug clearly stimulates breathing by a central action in or below the pons as its action is unaffected by brainstem transection in fetal lambs.[319] Doxapram speeds up awakening after halothane anesthesia,[320] as does physostigmine.[321] In dogs recovering from halothane anesthesia, this clinical observation was confirmed by electroencephalographic evidence of arousal after administration of each drug.[322]

Does Meperidine Have a Unique Antishivering Mechanism?

Finally, we return to the intriguing question: which pharmacologic properties of meperidine mediate its antishivering action? Meperidine is the only member of the opioid family that has clinically important local anesthetic activity in the dose range normally used for analgesia and is unique among currently used opioids in being effective as a sole agent for spinal anesthesia.[323] However, local anesthetic action does not appear to mediate the drug's antishivering action in humans since a clinical dose of intravenous lidocaine does not prevent shivering[324] or reduce the shivering threshold.[325]

Analgesic concentrations of meperidine produce considerable inhibition of 5-HT reuptake.[326] Meperidine, in combination with a monoamine oxidase inhibitor, can consequently cause fatal hyperthermia that is presumably caused by the accumulation of brain 5-HT.[327] The 50% inhibitory concentration of meperidine for 5-HT reuptake is 490 nM, but more than 100,000 nM for morphine.[328] Moreover, meperidine in analgesic doses is among the most potent inhibitors of norepinephrine reuptake in central neurons[326,329,330] and isolated nerve endings.[329,331] This effect is not inhibited by naloxone and is therefore not opioid receptor mediated.

Meperidine possesses several other nonopioid actions,[332] one or more of which may explain this drug's special antishivering action. For example, meperidine has noncompetitive NMDA receptor antagonist activity in the rat spinal cord.[333] Possible mechanisms by which NMDA antagonists interfere with shivering were previously discussed. Finally, does meperidine, as was claimed when it was introduced as an antispasmodic in 1939, have anticholinergic effects?[334] In the presence of a parasympathomimetic, meperidine is a competitive antagonist of muscarinic receptors in guinea-pig ileum.[335] Furthermore, meperidine shows significant muscarinic receptor binding in mice (K_I = 1.7 μM; Elmar Friderichs, M.D., written communication, June 28, 1999) However, recent data indicate that atropine slightly increases the threshold triggering shivering.[149]

An important recent contribution to the discussion on the mechanism by which meperidine inhibits postanesthetic shivering was made by Takada *et al.*[336] They transfected COS-7 cells with the cDNA for human α_{2A}, α_{2B}, and α_{2C} adrenoceptors. Results indicate that meperidine can bind to each of the α_2-adrenoceptor subtypes and transduces an agonist action at these sites. The α_{2B}-adrenoceptor subtype is the most sensitive and thus appears to be the most important receptor subtype in this regard. The next step is linking these pharmacologic findings to anatomic structures. However, the results are consistent with the possibility that meperidine exerts some antishivering action *via* α_2 adrenoceptors in the locus coeruleus.

Meperidine thus possesses special antishivering properties that are not shared by pure μ-receptor opioids. This special antishivering action is mediated by a shivering threshold that decreases twice as much as the vasoconstriction threshold[279] throughout the range of tested doses (table 1). κ-Opioid receptor agonists have antishivering effects, but nalbuphine comparably inhibits vasoconstriction and shivering[149]—suggesting that κ-opioid activity does not explain the special antishivering action of meperidine. Although meperidine has an anticholinergic action, this also does not appear to be the explanation for its singular antishivering efficacy. However, the explanation may involve its biogenic monoamine reuptake inhibition, NMDA receptor antagonism, or stimulation of α_2 adrenoceptors. The special antishivering action of meperidine may simply result from the drugs's lack of specificity and a fortunate accumulation of pharmacologic actions modulating thermoregulatory shivering.

Table 2. Pharmacologic Properties of Antishivering Drugs

	Opioid Receptor	NE Uptake	Alpha-2 Receptor	5-HT Uptake	5-HT Release	Dopamine Uptake	NMDA Receptor	Muscarinic Receptor	Arousal	Analgesia	Vasopressor Effect	Local Anesthetic Effect
Meperidine	(+) 273	(−) 329	(+) 336	(−) 328)		(−) 332	(−) 333	(−) 335		(+) 273	(+) 344	(+) 323
Butorphanol	(+) 282									(+) 284		
Nalbuphine	(+) 283									(+) 283	(+) 345	
Tramadol	(+) 192	(−) 192	(+) 195,196	(−) 191,214	(+) 191,214	(−) 193			(+) 189	(+) 189	(+) 346	(+) 190
Clonidine	ID 228		(+) 226					ID 229	(−) 197	(+) 197	(+) *	
Ketanserin		? 205	ID 208			? 205				(+) 206		
Physostigmine	ID 243,244				(+) 242			(+) 247	(+) 322	(+) 245	(+) 243	
Nefopam		(−) 187		(−) 187		(−) 187		(−)	(+) 186	(+) 347	(+) 347	
Methylphenidate		(−) 316,318		(−) 316,318		(−) 316,318			(+) 318	(+) 317	(+) 318	
Doxapram									(+) 320,322		(+) 319	
Orphenadrine							(−) 305	(−) 305		(+) 306		(+) 304
Ketamine	(+) 309	(−) 310		(−) 310		(−) 310	(−) 307	(−) 309		(+) 308	(+) 308	(+) 309

(+) stimulation/agonist; (−) inhibition/antagonist; ? suggested action; ID = indirect action.

* After intravenous administration, a transient increase in blood pressure precedes the hypotensive effect of α_2 agonists.

NE = norepinephrine; 5-HT = serotonin; DA = dopamine; NMDA = *N*-methyl-D-aspartate.

Conclusion

Because hypothermia is associated with shivering and so many other complications, surgical patients should be kept normothermic[337] unless hypothermia is specifically indicated for putative protection against cerebral ischemia[338–341] or spinal cord injury.[342] Given the discomfort and metabolic stress associated with shivering, treatment is appropriate in most cases. Any effective treatment for shivering will, by definition, reduce metabolic heat production and must be accompanied by an effective active heating system or a high ambient temperature.[343]

An inventory of the known antishivering drugs reveals striking similarities in their pharmacologic properties (table 2). However, conclusions should be cautiously extracted from this overview, because several drugs possess these mechanisms without any (known) thermoregulatory effect. Moreover, these common features are interrelated. Almost all antishivering drugs, for example, produce a transient vasopressor response.[243,308,318,319,344–347] On a theoretical basis, one cannot exclude that the presence of norepinephrine in the blood, resulting from a spillover from neuronal synapses, further increases the inhibition of cold defenses immediately after intravenous injection of the drug. Circulating catecholamines modulate the static and dynamic activities of skin cold receptors.[348,349]

In a classic article, Satinoff[23] postulated that thermoregulatory reflexes evolved out of systems that were originally used for other purposes, called "evolutionary coadaptation." He argued that it would be unnecessarily burdensome to require the evolutionary process to create new systems to solve a problem already solved by an existing system. For example, the peripheral vasomotor system first served as a supplemental respiratory organ in amphibians. It then became a heat collector and disperser in reptiles, and finally an essential thermoregulatory control mechanism in mammals. Similarly, the muscular organization in reptiles and the consequent changes in posture provided the basis for an internal heat production in mammals.

In place of the commonly held view of a single thermoregulatory integrator (*i.e.*, the preoptic area of the hypothalamus) with multiple inputs and outputs, modern concepts include integrators for each thermoregulatory response.[22] Furthermore, these integrators are distributed among numerous levels within the nervous system, with each being facilitated or inhibited by levels above and below.[23]

All antishivering drugs except ketanserin have weak or moderate analgesic properties in humans. The descending pain-control network acts pharmacologically through biogenic monoamines, and there is thought to be considerable interaction between antinociceptive and thermoregulatory systems.[55,215,350] Central aminergic systems exert a general modulatory influence on neurons involved in different functional and neuroendocrine systems.[39,351]

It thus seems reasonable to assume that thermoregulation is tightly linked to other homeostatic systems, including the control of pain. Pain and temperature signals are transmitted along similar fiber systems that synapse in dorsal horn regions. As mentioned previously, electrical stimulation of the rostral ventromedial medulla not only causes an increase in the analgesia to noxious stimuli, but also a decrease in the thermoregulatory response to peripheral warming and cooling.[215,352,353] One of the important functions of the rostral ventromedial medulla is to modulate the amount of pain and temperature input ascending from the spinal cord by gating the transmission of neuronal signals at the level of the dorsal horns.[137] This interesting expansion of the existing pain and thermoregulatory control models deserves further experimental investigation.

In summary, it is difficult to link pharmacologic properties to anatomic substrates and, specifically, to the control of thermoregulatory shivering. Even a partial understanding of the mechanisms involved in the shivering response reveals an extraordinary complexity, presumably the result of evolutionary coadaptation. No single structure or pathway is responsible for mediation of the thermoregulatory shivering response. In contrast, several mechanisms are able to modulate various thermoregulatory responses.

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