

# Perioperative Shivering

## Physiology and Pharmacology

Jan De Witte, M.D.,\* Daniel I. Sessler, M.D.†

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.<sup>1-7</sup> Although shivering is but one consequence of perioperative hypothermia, and rarely the most serious, it occurs frequently (*i.e.*, 40–60% after volatile anesthetics),<sup>8,9</sup> 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.<sup>10</sup> However, ev-

idence suggests that the majority of these ascending pathways terminate in the reticular formation<sup>11,12</sup> and that thermosensitive neurons exist at several regions outside the preoptic-anterior hypothalamus, including the ventromedial hypothalamus,<sup>13</sup> the midbrain,<sup>14-17</sup> the medulla oblongata,<sup>18,19</sup> and the spinal cord.<sup>20,21</sup> 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.<sup>22,23</sup>

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<sup>24-29</sup> and has been reviewed comprehensively.<sup>20</sup> Its ability to sense and modulate thermal signals was pivotal for development of the currently accepted multiple-input, multilevel concept of thermoregulation.<sup>22</sup> In fact, all thermoregulatory effector mechanisms are modulated by spinal cord temperature. In intact<sup>30</sup> and chronically spinalized<sup>31</sup> dogs and rabbits,<sup>32</sup> 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.<sup>33</sup>

**The Extrahypothalamic Brain Stem.** Thermosensitive sites that are not associated with defined anatomic structures appear to be dispersed in the lower brain stem.<sup>34</sup> Experiments in rats suggest that heat gain responses are powerfully regulated by a tonic inhibitory mechanism located in the midbrain and upper pons.<sup>35</sup> 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.<sup>14</sup> 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.<sup>12</sup>

\*Attending Anesthesiologist, Department of Anesthesia and Intensive Care, OLV Hospital. †Associate Dean for Research and Director, Outcomes Research™ Institute, Weakley Distinguished University Professor of Anesthesiology, University of Louisville, and Professor and Vice Chair, Ludwig Boltzmann Institute, University of Vienna.

Received from the Department of Anesthesia and Intensive Care, OLV Hospital, Aalst, Belgium; and the Outcomes Research™ Institute and Department of Anesthesiology, University of Louisville, Louisville, Kentucky. Submitted for publication January 1, 2000. Accepted for publication September 6, 2001. Supported by grant No. GM58273 from the National Institutes of Health, Bethesda, Maryland, and the Joseph Drown Foundation, Los Angeles, California.

Address reprint requests to Dr. De Witte: Department of Anesthesia and Intensive Care, OLV Hospital, Moorselbaan 164, Aalst 9300, Belgium. Address electronic mail to: jan.de.witte@olvz-aalst.be. On the World Wide Web: www.or.org. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

‡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.

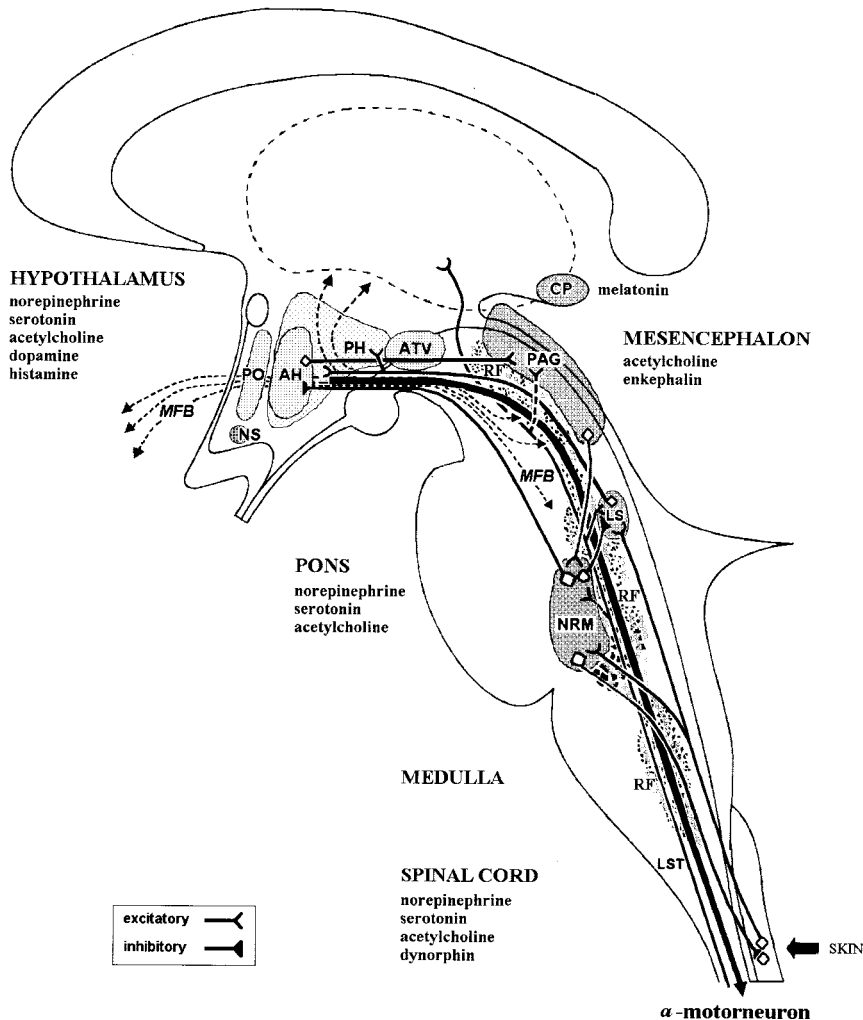


Fig. 1. Neural pathways in the control of shivering. The lateral spinothalamic tract projects to hypothalamic thermoregulatory centers and to nuclei in the pons and mesencephalon. The nucleus raphe magnus plays an important role in transmitting thermal information to the hypothalamus and has an inhibitory 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  $\alpha$  motor neurons. See text for a detailed explanation of the connecting pathways and neurochemical systems. CP = corpus pineale; MFB = medial forebrain bundle; NS = nucleus supra-chiasmaticus; 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.<sup>351</sup>

**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.<sup>18</sup> The locus subcoeruleus is a circumscribed area in the pons ventromedially to the locus coeruleus,<sup>36</sup> which contains the largest cluster of noradrenergic neurons in the brain.<sup>37</sup> The nucleus raphe magnus and the subcoeruleus area appear to be important relay stations in the transmission of thermal information from skin to hypothalamus.<sup>36,38</sup> These areas seem to be responsible for the modulation rather than the generation of thermal afferent information.<sup>39-41</sup>

#### Integration of Thermal Inputs

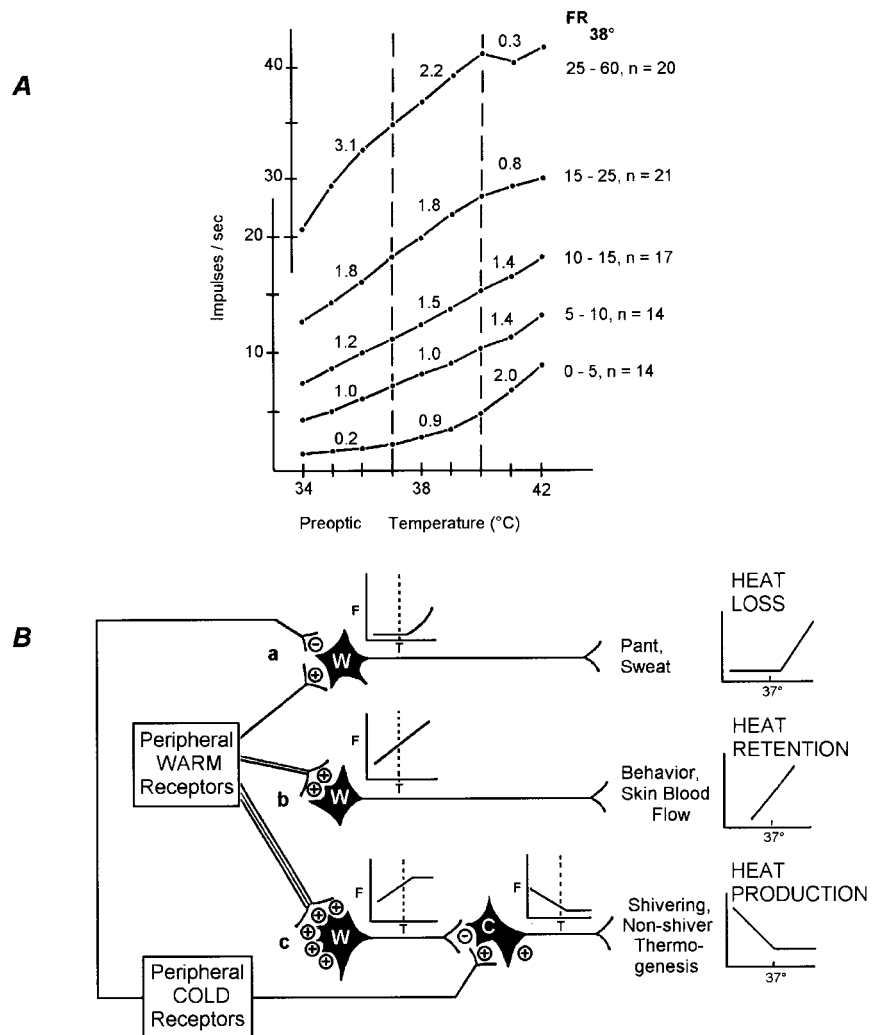
Most investigators accept that the preoptic region of the anterior hypothalamus is the dominant autonomic thermoregulatory controller in mammals. However, preoptic-anterior hypothalamus neurons also respond to nonthermal information, *e.g.*, reproductive hormones,<sup>42</sup> plasma osmolality,<sup>43-45</sup> glucose concentration,<sup>43,46</sup> blood pressure,<sup>47</sup> noxious stimuli,<sup>48</sup> carbon dioxide,<sup>49</sup> and emotional stimuli.<sup>50</sup> Much of the excitatory input to

warm-sensitive neurons in the preoptic-anterior hypothalamus comes from the hippocampus,<sup>51</sup> 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<sup>52</sup> and supra-chiasmatic nucleus activity,<sup>53</sup> 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.<sup>54</sup>

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



lant<sup>57</sup> 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.<sup>58</sup> In both animals<sup>59</sup> and humans,<sup>60</sup> 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.<sup>56,61</sup> Thermoregulatory vasoconstriction<sup>62</sup> decreases cutaneous heat loss<sup>63,64</sup> and constrains metabolic heat to the core

thermal compartment.<sup>65,66</sup> This usually prevents body temperature from decreasing the required additional 1°C required to activate intraoperative shivering.<sup>67-70</sup> 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<sup>71</sup> and in rodents, but its existence in adult humans is uncertain,<sup>72</sup> as it is not observed in anesthetized adults<sup>73</sup> or infants.<sup>74</sup>

**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.<sup>75</sup> However, a doubling of metabolic heat production is all that can be sustained over

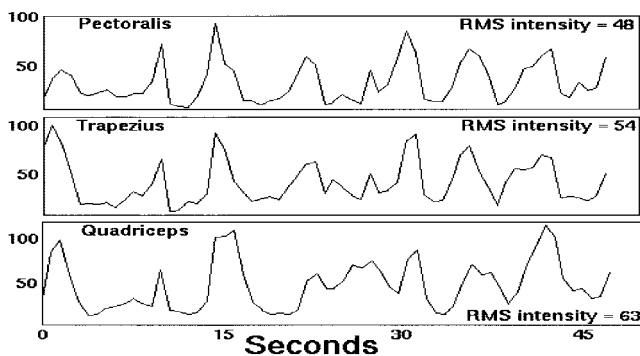


Fig. 3. Normal shivering is characterized by a 4–8 cycle/min “waxing-and-waning” pattern. Shivering intensity varies synchronously in widely distributed muscles, suggesting a central controller. Data are from Sessler *et al.*<sup>78</sup>

long periods.<sup>76</sup> 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).<sup>77,78</sup>

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

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

The larger  $\alpha$  motor neurons are more likely to manifest synchronized discharges than smaller ones.<sup>96</sup> Synchronization of motor neurons during shivering may be mediated by recurrent inhibition through Renshaw cells, a group of inhibitory interneurons identified in the cat.<sup>97,98</sup> Reflex activation of  $\alpha$  motor neurons *via* the  $\gamma$  muscle spindle loop (instability of the stretch reflex feedback system), is another potential but controversial

mechanism that could determine the rhythm and frequency of  $\alpha$  motor neurons discharges.<sup>99–101</sup>

## 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,<sup>102,103</sup> increases intraocular<sup>104</sup> and intracranial<sup>105</sup> pressures, and is especially disturbing to mothers during labor and delivery.<sup>106</sup>

Shivering can double or even triple oxygen consumption and carbon dioxide production, although the increases are typically much smaller.<sup>107,108</sup> 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<sup>109–111</sup> because age *per se* impairs normal thermoregulatory control.<sup>112–117</sup> 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.<sup>118,119</sup> 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.<sup>120</sup>

### *Abnormal Tremor Patterns*

Shivering is common in hypothermic patients recovering from general anesthesia.<sup>121–123</sup> 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<sup>122</sup> and that tremor occurs commonly in normothermic patients.<sup>124</sup> However, a subsequent study<sup>78</sup> 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<sup>125</sup> and in women having spontaneous term labor.<sup>126</sup>

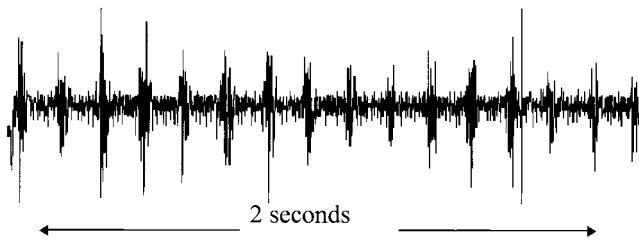


Fig. 4. A clonic tremor can be observed at low end-tidal concentrations of the volatile anesthetics (*i.e.*, 0.2–0.4% isoflurane). This tremor has a 5–7 Hz “bursting” electromyographic pattern that is identical to that produced by clonus after spinal cord transection. It is often accompanied by other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

Any increase in the thermoregulatory set-point (fever) may be associated with normal thermoregulatory shivering in normothermic or even hyperthermic patients.<sup>124,127</sup> 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.<sup>128</sup> 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.<sup>78</sup> 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.<sup>77</sup> 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.<sup>129</sup>

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.<sup>130</sup> 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<sup>52,131</sup> and depends on the state of vigilance<sup>52,132</sup> and cortical activity.<sup>133–135</sup>

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.<sup>136</sup> 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.<sup>137</sup> Similar results (no thermoresponses observed within a given electroencephalographic state) were obtained for single-unit activity in the subcoeruleus area.<sup>138</sup>

### 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.<sup>105,139–154</sup> 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.<sup>155,156</sup>

#### *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.<sup>157</sup> 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.<sup>158</sup>

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.<sup>159-161</sup> Contradictory results were reported for monoamines in a given species as well, and were attributed to differences in dosage,<sup>162</sup> microinjection technique,<sup>163</sup> ambient temperature,<sup>164,165</sup> and other factors.<sup>166</sup>

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.<sup>167</sup> 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.<sup>39,55,168</sup>

Norepinephrine microdialyzed into the preoptic area of conscious guinea pigs reduces core temperature, a reduction that is abolished by coadministration of the  $\alpha_2$ -adrenoceptor antagonists yohimbine and rauwolscine.<sup>169</sup> The  $\alpha_2$ -adrenoceptor agonist clonidine evokes dose-dependent reductions in core temperature, whereas  $\alpha_1$ -,  $\beta_1$ -, and  $\beta_2$ -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,<sup>170</sup> whereas decreasing the ambient temperature to 2°C markedly reduces the norepinephrine release from the preoptic-anterior hypothalamic area of the rat.<sup>171</sup>

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.<sup>172</sup> When 5-HT is injected into the rostral hypothalamus of cats, hyperthermia associated with shivering is evoked.<sup>172</sup> In rat midbrain slice preparations, the majority of warm-sensitive units and all cold-sensitive units are inhibited by 5-HT.<sup>173</sup> In contrast, 5-HT activates the ma-

majority of temperature-sensitive units in the medulla oblongata of the rat.<sup>173</sup>

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.<sup>168</sup> In different physiologic situations, *e.g.*, during cold adaptation or during fever, the interthreshold range (temperatures between the sweating and shivering thresholds) widens or

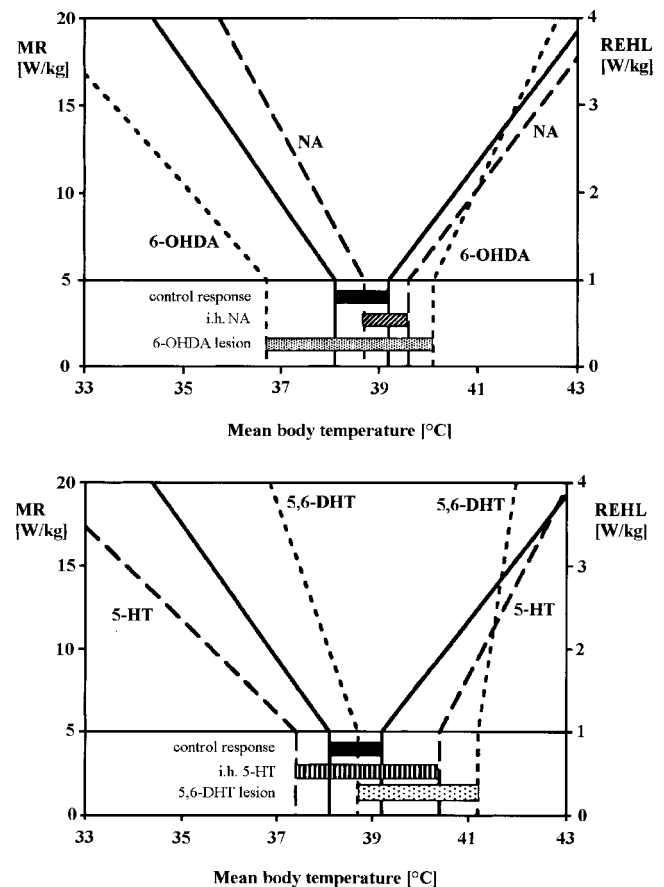


Fig. 5. Antagonistic brain stem modulatory inputs change the threshold and gain of thermoregulatory responses in guinea pigs. The horizontal line at the metabolic rate (MR) of 5 W/kg denotes the normal value measured at thermoneutral ambient temperature. Intrahypothalamic (i.h.) microinjection of noradrenaline (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.<sup>168</sup>

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).<sup>174</sup> 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.<sup>175</sup> Despite multiple confounding factors, there is increasing evidence for the involvement of monoaminergic brain systems in adaptive changes in thermoregulation (fig. 5).<sup>55,161</sup>

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

Histaminergic pathways also may be involved in central thermoregulation, *via* both H<sub>1</sub> and H<sub>2</sub> histamine receptors, as demonstrated in behavioral studies.<sup>182-184</sup> There is some evidence for histaminergic pathways in the rostral hypothalamus involved in thermoregulation and integration with other monoaminergic thermoregulatory pathways, as reviewed previously.<sup>185</sup>

**Drug Effects.** Nefopam,<sup>186</sup> an analgesic with powerful antishivering properties,<sup>105</sup> is a potent inhibitor of synaptic uptake of 5-HT, norepinephrine, and dopamine,<sup>187</sup> and slightly lowers normal body temperature.<sup>188</sup> Tramadol<sup>189,190</sup> is an antishivering drug<sup>146</sup> with a similar mechanism of action: it inhibits the reuptake of 5-HT,<sup>191</sup> norepinephrine,<sup>192</sup> and dopamine<sup>193</sup> and facilitates 5-HT release.<sup>191</sup> Despite different degrees of opioid-like characteristics in preclinical tests,<sup>192</sup> tramadol lacks significant naloxone reversibility in humans.<sup>194,195</sup> In human volunteers, a high dose of naloxone only partially reverses the antishivering effect of tramadol.<sup>146</sup> Cerebral  $\alpha_2$  adrenoceptors are thought to play a role in the attenuation of postoperative shivering by tramadol.<sup>196</sup>

$\alpha_2$ -Adrenergic agonists<sup>197</sup> hyperpolarize neurons, presumably by increasing potassium conductance through G<sub>i</sub>-coupled proteins.<sup>198,199</sup> This, in turn, suppresses neuronal firing,<sup>200</sup> which is linked to the range of thermo-

sensitivity.<sup>57</sup> Furthermore, activation of  $\alpha_2$ -adrenoceptors suppresses N-type calcium entry into nerve cells,<sup>200</sup> which depresses neurotransmitter release.<sup>201</sup> A greater retention of Ca<sup>2+</sup> ions on the neuron's surface stabilizes the cell membrane and lowers the firing rate of heat gain units in the posterior hypothalamus.<sup>202</sup>

The antihypertensive drug ketanserin also interferes with postanesthetic shivering; however, the efficacy of ketanserin is rather low.<sup>141,203</sup> Ketanserin is an antagonist with high affinity for both 5-HT<sub>2</sub> receptors<sup>204,205,206</sup> and  $\alpha_1$  adrenoceptors.<sup>207,208</sup> Similar to other  $\alpha_1$ -adrenoceptor antagonists (e.g., prazosin), ketanserin acts indirectly *via* facilitation of a central presynaptic  $\alpha_2$ -adrenoceptor mechanism in the lower brainstem.<sup>208</sup>

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.<sup>154,209</sup> There are almost no animal data available about 5-HT<sub>3</sub> receptor-mediated temperature-regulating mechanisms.<sup>210</sup>

**Sites of Action.** The effects of nefopam<sup>187</sup> and tramadol<sup>191,192</sup> 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.<sup>211</sup> The locus coeruleus appears to be a proshivering center that activates heat production in rodents.<sup>55</sup> The locus coeruleus is also the main noradrenergic nucleus involved in the descending pain-control system,<sup>212</sup> with its activity regulated by  $\alpha_2$  autoreceptors.  $\alpha_2$ -HT<sub>1A</sub> receptors modulate responses mediated by  $\alpha_{2A}$  adrenoceptors in the locus coeruleus.<sup>213</sup> In humans,  $\alpha_2$ -adrenoceptor antagonism with yohimbine significantly reverses the analgesic effects of tramadol.<sup>195</sup>

Racemic tramadol and its (+) enantiomer significantly reduce 5-HT uptake and increase stimulated 5-HT efflux in the dorsal raphe nucleus.<sup>214</sup> 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.<sup>212</sup> The nucleus raphe magnus is an antishivering center that activates heat loss mechanisms and inhibits thermogenesis during cold adaptation.<sup>55,215</sup> 5-HT is the major neurotransmitter in the raphe nuclei, but half of the raphe cells that project to the spinal cord are not serotonergic.<sup>216</sup> There is also a significant amount of norepinephrine in the nucleus raphe magnus, and approximately 10% of nucleus raphe magnus serotonergic cells express  $\alpha_2$  adrenoceptors.<sup>217</sup>

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.<sup>40</sup> 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  $\alpha_2$ -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.<sup>38</sup> 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.<sup>218</sup> Just as descending inhibition restricts transmission of pain signals, efferents to the dorsal horn of the spinal cord may inhibit cutaneous thermal input.<sup>215,219,220</sup> However, this assumption remains controversial.<sup>221</sup> In the very least, descending 5-HT terminals from the locus coeruleus make intimate contact with motor neurons, mostly *via* cord internun- tials.<sup>222-224</sup> However, the role of these nerve terminals in the modulation of shivering remains to be established.

An anatomic target for the antishivering effect of  $\alpha_2$ -adrenergic agonists can be found at three levels. First, a small intravenous dose of clonidine reduces the spontaneous firing rate in the locus coeruleus<sup>225</sup> and indirectly reduces norepinephrine-induced firing of serotonergic neurons in the dorsal raphe nucleus.<sup>226</sup> Second, the action of  $\alpha_2$ -adrenergic agonists in the locus coeruleus may also increase activation of  $\alpha_2$  adrenoceptors in the spinal cord.<sup>227</sup> Intrathecal  $\alpha_2$ -adrenergic agonists are known to release dynorphin (a  $\kappa$ -opioid agonist)<sup>228</sup> and to stimulate norepinephrine and acetylcholine release.<sup>229</sup> Dynorphin is present in high concentration in the spinal cord<sup>230</sup> 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.<sup>215</sup> Third, the hypothalamus contains a high density of  $\alpha_2$  adrenoceptors. Norepinephrine microdialyzed into the hypothalamus, for example, activates  $\alpha_2$  adrenoceptors, reduces metabolic heat production, and produces hypothermia.<sup>169</sup> Pretreatment of the preoptic-anterior hypothalamic area with the selective  $\alpha_2$ -adrenoceptor agonist yohimbine inhibited the hypothermic response of clonidine.<sup>231</sup>

#### *Cholinomimetics*

**Pharmacologic Evidence.** In single-unit studies of the preoptic-anterior hypothalamus in cats,<sup>232</sup> rats,<sup>233</sup> and many other species,<sup>161</sup> the effect of acetylcholine on thermosensitive neurons remains inconclusive. The muscarinic or nicotinic cholinergic receptors 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.<sup>176,234</sup> 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 shiv-

ering and causes hypothermia,<sup>235</sup> whereas rats become hyperthermic when atropine is injected into the hypothalamus.<sup>236</sup> In rabbits, intravenous injection of nicotine stops shivering.<sup>237</sup>

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.<sup>238</sup> 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.<sup>161,176</sup>

In the brain stem, cholinergic receptors also may participate in thermoregulation, interacting with monoaminergic and peptidergic systems. Microinjection of the cholinergic 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.<sup>239</sup> 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.<sup>240</sup>

**Drug Effects.** Physostigmine is as effective in preventing postanesthetic shivering as meperidine and clonidine.<sup>144</sup> 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,<sup>241</sup> but serotonergic receptors<sup>242</sup> and an endorphinergic mechanism<sup>243,244</sup> may also be involved. Analgesia after intrathecal administration of anticholinesterase is mediated through muscarinic receptors, and there is a synergistic interaction with intrathecal  $\mu$ -opioid and  $\alpha_2$ -adrenergic agonists.<sup>245</sup> 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.<sup>246</sup> 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<sub>2</sub>-dopamine receptor antagonist. Recent data indi-



cate that atropine slightly increases the thresholds triggering vasoconstriction and shivering,<sup>149</sup> which is consistent with the premedication study.

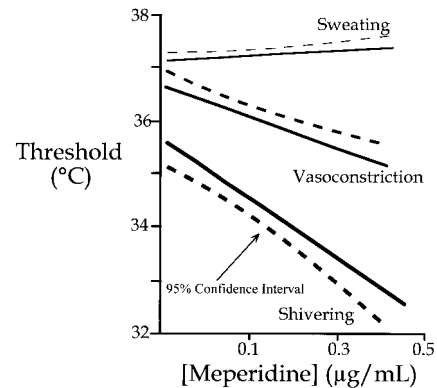
**Sites of Action.** There are numerous potential anatomic substrates for the antishivering effect of physostigmine, situated at both supraspinal and spinal levels. In addition to the major cholinergic nuclei and pathways, cholinergic interneurons are found throughout the central nervous system.<sup>247</sup> Furthermore, functional interactions between the adrenergic and muscarinic systems are well established.<sup>245,248</sup> Most prominently, there are serotonergic afferents from the raphe nuclei that project to cholinergic brain stem nuclei.<sup>249</sup> Through dual projections, cholinergic and aminergic brainstem neurons can concurrently modulate the activity of neurons in the thalamus and basal forebrain during cortical arousal.<sup>250</sup> 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.<sup>251</sup> 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.<sup>252,253</sup> In contrast, hypothermia-producing substances (angiotensin II<sup>254</sup> and morphine<sup>255</sup>) excite and inhibit the activity of preoptic-anterior warm-sensitive and cold-sensitive neurons, respectively. Poikilothermia-producing peptides such as bombesin and neurotensin<sup>256</sup> 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, adrenocorticotrophic hormone, and  $\alpha$ -melanocyte stimulating hormone are thought to act as endogenous antipyretics during fever.<sup>257,258</sup>

Opioid peptides induce changes in body temperature that depend on the species, dose, ambient temperature, and degree of restraint during testing.<sup>259</sup> Met-enkephalin and  $\beta$ -endorphin induce hyperthermia when given intracerebroventricularly in a low dose, the precise mechanism being unclear.<sup>260</sup> At higher doses, enkephalin and  $\beta$ -endorphin cause hypothermia, probably because of a reduction in metabolic heat production.<sup>261,262</sup> Microinjected into the preoptic-anterior hypothalamus or the periaqueductal gray,  $\beta$ -endorphin evokes hyperther-



**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 =  $-3.0^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}^{-1}$ ). Meperidine decreased the shivering threshold nearly twice as much as the vasoconstriction threshold (slope =  $-5.6^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}^{-1}$ ). 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.*<sup>279</sup>

mia,<sup>263,264</sup> as does the injection of enkephalin into the preoptic-anterior hypothalamus.<sup>265</sup> Infusion of  $\beta$ -endorphin into the lateral cerebral ventricle of the rat, however, causes hypothermia.<sup>266</sup>

**Drug Effects.** Pure  $\mu$ -receptor agonists, including morphine (2.5 mg), fentanyl (25  $\mu\text{g}$ ), and alfentanil (250  $\mu\text{g}$ ), may be significantly better treatments for post-anesthetic shivering than placebo.<sup>267–269</sup> Alfentanil is probably effective because increasing plasma concentrations linearly reduce the shivering threshold.<sup>70,270</sup> Epidurally administered sufentanil in patients produces a dose-dependent decrease in shivering response and body temperature.<sup>271</sup> Epidural fentanyl also reduced the shivering threshold when added to lidocaine for epidural anesthesia.<sup>272</sup>

Meperidine<sup>273</sup> is not only an effective treatment for shivering,<sup>274–278</sup> but the drug is clearly more effective than equianalgesic concentrations of pure  $\mu$ -receptor agonists.<sup>70,276</sup> Meperidine decreases the shivering threshold almost twice as much as the vasoconstriction threshold (fig. 6).<sup>279</sup> This is in distinct contrast to other analgesic and sedative drugs, including propofol,<sup>67</sup> dexmedetomidine,<sup>152</sup> and midazolam<sup>280</sup> (table 1), and to general anesthetics.<sup>68,69</sup> The gain and maximum intensity of shivering remain unchanged during both alfentanil and meperidine administration.<sup>70,279</sup> 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  $\kappa$ -opioid receptors.<sup>145</sup> Consistent with this theory, nalbuphine and butorphanol, two other antishivering drugs,<sup>140,149,153,281</sup> are known to have  $\kappa$ -opioid receptor activity.<sup>282–284</sup> 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	$-6.1^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	$-3.3^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	1.85
Tramadol	$-4.2^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	$-3.0^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	1.40
Alfentanil	$-0.0057^{\circ}\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$	$-0.0049^{\circ}\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$	1.16
Nalbuphine	$-2.8^{\circ}\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$	$-2.6^{\circ}\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$	1.08
Dexmedetomidine	$-2.4^{\circ}\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$	$-1.61^{\circ}\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$	1.49
Propofol	$-0.7^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	$-0.6^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	1.17
Midazolam	$-2.0^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	$-2.67^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$	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  $\alpha_2$ -agonist, are comparable. Nalbuphine, a  $\kappa$ -opioid receptor agonist, seems to have no special anti-shivering effect. Data are from Kurz,<sup>279</sup> De Witte,<sup>146</sup> Kurz,<sup>70</sup> Greif,<sup>149</sup> Talke,<sup>152</sup> Matsukawa,<sup>67</sup> Kurz.<sup>280</sup>

ory is that recent data indicate that nalbuphine, a mixed  $\mu$ -antagonist and  $\kappa$ -agonist, comparably reduces the vasoconstriction and shivering threshold in volunteers.<sup>149</sup>

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

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

### Cations

The positive ions calcium ( $\text{Ca}^{2+}$ ) and sodium ( $\text{Na}^{+}$ ) may play a functionally opposing role in mediation of body temperature.<sup>161</sup> In monkeys,<sup>294</sup> perfusion of excess  $\text{Ca}^{2+}$  into the posterior hypothalamus evokes a decrease in body temperature, whereas perfusion with  $\text{Na}^{+}$  ions increases body temperature. The magnitude of this response depends on the ratio of the cations' concentration<sup>295</sup> 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.<sup>202</sup> 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.<sup>296,297</sup>

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.<sup>298</sup> Magnesium chloride injected into the third ventricle of the sheep increases body temperature,<sup>299</sup> whereas intracerebroventricular injection of  $\text{Ca}^{2+}$  elicits hypothermia in other species.<sup>300</sup> During cold exposure, magnesium concentration in rat plasma increases,<sup>301</sup> and in heat-acclimated volunteers, plasma magnesium decreases.<sup>302</sup> In addition, during treatment with magnesium sulfate, a significant decrease in maternal temperature was observed.<sup>303</sup> 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<sup>295</sup> and was recently found to stop postanesthetic shivering.<sup>147</sup> Several antishivering drugs share the NMDA receptor antagonist properties of magnesium.

Orphenadrine is both antimuscarinic<sup>304</sup> and has non-competitive NMDA receptor antagonist properties.<sup>305</sup> Orphenadrine extends the action of perioperative analgesics<sup>306</sup> and thus has been proposed as an alternative to methylphenidate to control postanesthetic shivering.<sup>148</sup>

Ketamine, which is a competitive NMDA receptor antagonist,<sup>307</sup> also inhibits postanesthetic shivering<sup>143</sup>; 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,<sup>308</sup> including being a  $\kappa$ -opioid agonist,<sup>309</sup> blocking amine uptake in the descending inhibitory monoaminergic pain pathways,<sup>310,311</sup> having a local anesthetic action, and having an interaction with muscarinic receptors.<sup>309</sup>

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.<sup>312</sup> Furthermore, NMDA receptors modulate noradrenergic and serotonergic neurons in the locus coeruleus.<sup>313,314</sup> In the dorsal raphe nucleus, 5-HT acts as a neuromodulator to enhance the effects of NMDA receptors.<sup>286</sup> Finally, the NMDA receptors at the dorsal horn of the spinal cord modulate ascending nociceptive transmission.<sup>293</sup> 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.<sup>139,315</sup> 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.<sup>316,317</sup> Activation of the raphe system and the concomitant arousal<sup>318</sup> 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.<sup>142</sup> 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.<sup>319</sup> Doxapram speeds up awakening after halothane anesthesia,<sup>320</sup> as does physostigmine.<sup>321</sup> In dogs recovering from halothane anesthesia, this clinical observation was confirmed by electroencephalographic evidence of arousal after administration of each drug.<sup>322</sup>

### **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.<sup>323</sup> 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<sup>324</sup> or reduce the shivering threshold.<sup>325</sup>

Analgesic concentrations of meperidine produce considerable inhibition of 5-HT reuptake.<sup>326</sup> Meperidine, in combination with a monoamine oxidase inhibitor, can consequently cause fatal hyperthermia that is presumably caused by the accumulation of brain 5-HT.<sup>327</sup> The

50% inhibitory concentration of meperidine for 5-HT reuptake is 490 nM, but more than 100,000 nM for morphine.<sup>328</sup> Moreover, meperidine in analgesic doses is among the most potent inhibitors of norepinephrine reuptake in central neurons<sup>326,329,330</sup> and isolated nerve endings.<sup>329,331</sup> This effect is not inhibited by naloxone and is therefore not opioid receptor mediated.

Meperidine possesses several other nonopioid actions,<sup>332</sup> 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.<sup>333</sup> 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?<sup>334</sup> In the presence of a parasympathomimetic, meperidine is a competitive antagonist of muscarinic receptors in guinea-pig ileum.<sup>335</sup> Furthermore, meperidine shows significant muscarinic receptor binding in mice ( $K_I = 1.7 \mu\text{M}$ ; Elmar Friderichs, M.D., written communication, June 28, 1999). However, recent data indicate that atropine slightly increases the threshold triggering shivering.<sup>149</sup>

An important recent contribution to the discussion on the mechanism by which meperidine inhibits postanesthetic shivering was made by Takada *et al.*<sup>336</sup> They transfected COS-7 cells with the cDNA for human  $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$  adrenoceptors. Results indicate that meperidine can bind to each of the  $\alpha_2$ -adrenoceptor subtypes and transduces an agonist action at these sites. The  $\alpha_{2B}$ -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*  $\alpha_2$  adrenoceptors in the locus coeruleus.

Meperidine thus possesses special antishivering properties that are not shared by pure  $\mu$ -receptor opioids. This special antishivering action is mediated by a shivering threshold that decreases twice as much as the vasoconstriction threshold<sup>279</sup> throughout the range of tested doses (table 1).  $\kappa$ -Opioid receptor agonists have antishivering effects, but nalbuphine comparably inhibits vasoconstriction and shivering<sup>149</sup>—suggesting that  $\kappa$ -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  $\alpha_2$  adrenoceptors. The special antishivering action of meperidine may simply result from the drugs' 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  $\alpha_2$  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<sup>337</sup> unless hypothermia is specifically indicated for putative protection against cerebral ischemia<sup>338-341</sup> or spinal cord injury.<sup>342</sup> 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.<sup>343</sup>

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.<sup>243,308,318,319,344-347</sup> 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.<sup>348,349</sup>

In a classic article, Satinoff<sup>23</sup> 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 mus-

cular 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.<sup>22</sup> Furthermore, these integrators are distributed among numerous levels within the nervous system, with each being facilitated or inhibited by levels above and below.<sup>23</sup>

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.<sup>55,215,350</sup> Central aminergic systems exert a general modulatory influence on neurons involved in different functional and neuroendocrine systems.<sup>39,351</sup>

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.<sup>215,352,353</sup> 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.<sup>137</sup> This interesting expansion of the existing pain and thermoregulatory control models deserves further experimental investigation.

In summary, it is difficult to link pharmacologic prop-

erties 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.

The authors thank Elmar Friderichs, M.D. (Department of Pharmacology, Grüenthal GmbH, Aachen, Germany), and colleagues for discussing pharmacologic topics in this manuscript.

## References

- Frank SM, Beattie C, Christopherson R, Norris EJ, Rock P, Parker S, Kimball AW: Epidural versus general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothermia. *ANESTHESIOLOGY* 1992; 77:252-7
- Morris RH, Wilkey BR: The effects of ambient temperature on patient temperature during surgery not involving body cavities. *ANESTHESIOLOGY* 1970; 32:102-7
- Morris RH: Influence of ambient temperature on patient temperature during intraabdominal surgery. *Ann Surg* 1971; 173:230-3
- Morris RH: Operating room temperature and the anesthetized, paralyzed patient. *Surgery* 1971; 102:95-7
- Kurz A, Kurz M, Poeschl G, Faryniak B, Redl G, Hackl W: Forced-air warming maintains intraoperative normothermia better than circulating-water mattresses. *Anesth Analg* 1993; 77:89-95
- Kurz A, Sessler DI, Narzt E, Lenhart R: Morphometric influences on intraoperative core temperature changes. *Anesth Analg* 1995; 80:562-7
- Kurz A, Sessler DI, Narzt E, Bekar A, Lenhardt R, Huemer G: Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia. *J Clin Anesth* 1995; 7:359-66
- De Witte J, Deloof T, De Veylder J, Housmans PR: Tramadol in the treatment of postanesthetic shivering. *Acta Anaesthesiol Scand* 1997; 41:506-10
- Horn E-P, Werner C, Sessler DI, Steinfath M, Schulte am Esch J: Late intraoperative administration of clonidine prevents postanesthetic shivering after total intravenous or volatile anesthesia. *Anesth Analg* 1997; 84:613-7
- Barbour HG: Die Wirkung unmittelbarer Erwärmung und Abkühlung der Wärmezentra auf die Körpertemperatur. *Arch Exp Pathol Pharmacol* 1912; 70: 1-15
- Mehler WH, Feferman ME, Nauta WJH: Ascending axon degeneration following anterolateral cordotomy: An experimental study in the monkey. *Brain* 1960; 83:718-50
- Crawshaw LI, Wollmuth LP, O'Connor CS, Rausch RN, Simpson L: Body temperature regulation in vertebrates: Comparative aspects and neuronal elements, Thermoregulation: Physiology and Biochemistry. Edited by Schönbaum E, Lomax P. New York, Pergamon Press, 1990, pp 209-20
- Hori T, Kuriyama K, Nakashima T: Thermal responsiveness of neurons in the ventromedial hypothalamus (letter). *J Physiol Soc Jpn* 1988; 50:619
- Asami T, Hori T, Kiyohara T, Nakashima T: Convergence of thermal signals on the reticulospinal neurons in the midbrain, pons and medulla oblongata. *Brain Res Bull* 1988; 20:581-96
- Nakayama T, Hardy JD: Unit responses in the rabbit's brain stem to changes in brain and cutaneous temperature. *J Appl Physiol* 1969; 27:848-57
- Hori T, Harada Y: Midbrain neuronal responses to local and spinal cord temperatures. *Am J Physiol* 1976; 231:1573-8
- Hori T, Harada Y: Responses of midbrain raphe neurons to local temperature. *Pflügers Arch* 1976; 364:205-7
- Dickenson AH: Specific responses of rat raphe neurons to skin temperature. *J Physiol* 1977; 273:277-93
- Inoue S, Murakami N: Unit responses in the medulla oblongata of rabbit to changes in local and cutaneous temperature. *J Physiol (Lond)* 1976; 259:339-56
- Cabanac M: Temperature regulation. *Annu Rev Physiol* 1975; 37:415-39
- Simon E, Iriki M: Sensory transmission of spinal heat and cold sensitivity in ascending spinal neurons. *Pflügers Arch* 1971; 328:103-20
- Pehl U, Simon E, Schmid HA: Properties of spinal neuronal thermosensitivity in vivo and in vitro. *Ann N Y Acad Sci* 1997; 813:138-45
- Satinoff E: Neural organization and evolution of thermal regulation in mammals. *Science* 1978; 201:16-22
- Simon E: Temperature regulation: The spinal cord as a site of extrahypothalamic thermoregulatory functions. *Rev Physiol Biochem Pharmacol* 1974; 71:1-76
- Guieu JD, Hardy JD: Effects of heating and cooling of the spinal cord on preoptic unit activity. *J Appl Physiol* 1970; 29:675-83
- Chambers WW, Seigel MS, Liu JC, Liu CN: Thermoregulatory responses of decerebrate and spinal cats. *Exp Neurol* 1974; 42:282-99
- Bacon M, Bligh J: Interaction between the effects of spinal heating and cooling and of injections into a lateral cerebral ventricle of noradrenaline, 5-hydroxytryptamine and carbachol on thermoregulation in sheep. *J Physiol (Lond)* 1976; 254:213-27
- Banet M, Hensel H, Liebermann H: The central control of shivering and non-shivering thermogenesis in the rat. *J Physiol (Lond)* 1978; 283:569-84
- Boulant JA, Hardy JD: The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. *J Physiol (Lond)* 1974; 240:639-60
- Simon E, Rautenberg W, Thauer R, Iriki M: Die Auslösung von Kältezittern durch lokale Kühlung im Wirbelkanal. *Pflügers Arch* 1964; 281:309-31
- Simon E, Klusmann FW, Rautenberg W, Kosaka M: Kältezittern bei narkotisierten spinalen Hunden. *Pflügers Arch* 1966; 291:187-204
- Kosaka M, Simon E, Thauer R: Shivering in intact and spinal rabbits during spinal cord cooling. *Experientia* 1967; 23:385-7
- Schmidt KD, Chan CW: Thermoregulation and fever in normal persons and in those with spinal cord injuries. *Mayo Clin Proc* 1992; 67:469-75
- Schmiege G, Mercer JB, Jessen C: Thermosensitivity of the extrahypothalamic brain stem in conscious goats. *Brain Res* 1980; 188:383-97
- Amini-Sereshtki L, Zarrindast MR: Brain stem tonic inhibition of thermoregulation in the rat. *Am J Physiol* 1984; 247:R154-9
- Hinckel P, Schröder-Rosenstock K: Responses of pontine units to skin-temperature changes in the guinea-pig. *J Physiol* 1981; 314:189-94
- Foot SL, Bloom FE, Aston-Jones G: Nucleus locus coeruleus: new evidence of anatomical and physiological specificity. *Physiol Rev* 1983; 63:844-914
- Brück K, Hinckel P: Thermoregulatory noradrenergic and serotonergic pathways to hypothalamic units. *J Physiol* 1980; 304:193-202
- Zeisberger E, Roth J: Central regulation of adaptive responses to heat and cold, *Handbook of Physiology*. Section 4: Environmental Physiology. Edited by Fregly MJ, Blatteis CM. New York, Oxford, Oxford University Press, 1996, pp 579-95
- Sato H: Raphe-spinal and subcoeruleo-spinal modulation of temperature signal transmission in rats. *J Therm Biol* 1993; 18:211-21
- Berner NJ, Grahn DA, Heller HC: 8-OH-DPAT-sensitive neurons in the nucleus raphe magnus modulate thermoregulatory output in rats. *Brain Res* 1999; 831:155-64
- Silva NL, Boulant JA: Effects of testosterone, estradiol, and temperature on neurons in preoptic tissue slices. *Am J Physiol* 1986; 250:R625-32
- Silva NL, Boulant JA: Effects of osmotic pressure, glucose, and temperature on neurons in preoptic tissue slices. *Am J Physiol* 1984; 247:R335-45
- Nakashima T, Hori T, Kiyohara T, Shibata M: Osmosensitivity of preoptic thermosensitive neurons in hypothalamic slices in vitro. *Pflügers Arch* 1985; 405:112-7
- Koga H, Hori T, Inoue T, Kiyohara T, Nakashima T: Convergence of hepatoportal osmotic and cardiovascular signals on preoptic thermosensitive neurons. *Brain Res Bull* 1987; 19:109-13
- Boulant JA, Silva NL: Interactions of reproductive steroids, osmotic pressure and glucose on thermosensitive neurons in preoptic tissue slices. *Can J Physiol Pharmacol* 1987; 65:1267-73
- Koga H, Hori T, Kiyohara T, Nakashima T: Responses of preoptic thermosensitive neurons to changes in blood pressure. *Brain Res Bull* 1987; 18:749-55
- Kanosue K, Nakayama T, Ishikawa Y, Imai-Matsumura K: Responses of hypothalamic and thalamic neurons to noxious and scrotal thermal stimulations in rats. *J Therm Biol* 1984; 9:11-3
- Tamaki Y, Nakayama T, Matsumura K: Effects of carbon dioxide inhalation on preoptic thermosensitive neurons. *Pflügers Arch* 1986; 407:8-13
- Hori T, Kiyohara T, Shibata M, Oomura Y, Nishino H, Aou S, Fujita I: Responsiveness of monkey preoptic thermosensitive neurons to non-thermal emotional stimuli. *Brain Res Bull* 1986; 17:75-82
- Boulant JA, Demieville HN: Responses of thermosensitive preoptic and septal neurons to hippocampal and brain stem stimulation. *J Neurophysiol* 1977; 40:1356-68
- Glantz SF, Heller HC: Changes in the thermal characteristics of hypothalamic neurons during sleep and wakefulness. *Brain Res* 1984; 309:17-26
- Derambure PS, Boulant JA: Circadian thermosensitive characteristics of suprachiasmatic neurons in vitro. *Am J Physiol* 1994; 266:R1876-84
- Hori T, Katafuchi T: Cell biology and the functions of thermosensitive neurons in the brain. *Prog Brain Res* 1998; 115:9-23
- Brück K, Zeisberger E: Adaptive changes in thermoregulation and their neuropharmacological basis, *Thermoregulation: Physiology and Biochemistry*. Edited by Schönbaum E, Lomax P. New York, Pergamon Press, 1990, pp 255-307
- Boulant JA: Hypothalamic neurons regulating body temperature, *Handbook of Physiology*. Section 4: Environmental Physiology. Edited by Fregly MJ, Blatteis CM. New York, Oxford, Oxford University Press, 1996, pp 105-26
- Boulant JA: The effect of firing rate on preoptic neuronal thermosensitivity. *J Physiol* 1974; 240:661-9
- Jessen C: Interaction of body temperatures in control of thermoregulatory effector mechanisms, *Handbook of Physiology*. Section 4: Environmental Physiology. Edited by Fregly MJ, Blatteis CM. New York, Oxford, Oxford University Press, 1996, pp 127-38

59. Banet M, Hensel H: Nonshivering thermogenesis induced by repetitive hypothalamic cooling in the rat. *Am J Physiol* 1976; 230:522-6
60. Sessler DI: Current concept: Mild perioperative hypothermia. *N Engl J Med* 1997; 336:1730-7
61. Webb P: The physiology of heat regulation. *Am J Physiol* 1995; 37:R838-50
62. Hales JRS: Skin arteriovenous anastomoses, their control and role in thermoregulation, Cardiovascular Shunts: Phylogenetic, Ontogenetic and Clinical Aspects. Edited by Johansen K, Burggren W. Copenhagen, Munksgaard, 1985, pp 433-51
63. Sessler DI, Moayeri A, Støen R, Glosten B, Hynson J, McGuire J: Thermoregulatory vasoconstriction decreases cutaneous heat loss. *ANESTHESIOLOGY* 1990; 73:656-60
64. Sessler DI, Hynson J, McGuire J, Moayeri A, Heier T: Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases heat loss. *ANESTHESIOLOGY* 1992; 76:670-5
65. Kurz A, Sessler DI, Christensen R, Dechert M: Heat balance and distribution during the core-temperature plateau in anesthetized humans. *ANESTHESIOLOGY* 1995; 83:491-9
66. Belani K, Sessler DI, Sessler AM, Schroeder M, McGuire J, Washington D, Moayeri A: Leg heat content continues to decrease during the core temperature plateau in humans. *ANESTHESIOLOGY* 1993; 78:856-60
67. Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C: Propofol linearly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 82:1169-80
68. Annadata RS, Sessler DI, Tayfeh F, Kurz A, Dechert M: Desflurane slightly increases the sweating threshold, but produces marked, non-linear decreases in the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 83:1205-11
69. Xiong J, Kurz A, Sessler DI, Plattner O, Christensen R, Dechert M, Ikeda T: Isoflurane produces marked and non-linear decreases in the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1996; 85:240-5
70. Kurz A, Go JC, Sessler DI, Kaer K, Larson M, Bjorksten AR: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 83:293-9
71. Dawkins MJR, Scopes JW: Non-shivering thermogenesis and brown adipose tissue in the human new-born infant. *Nature* 1965; 206:201-2
72. Jessen K: An assessment of human regulatory nonshivering thermogenesis. *Acta Anaesthesiol Scand* 1980; 24:138-43
73. Hynson JM, Sessler DI, Moayeri A, McGuire J: Absence of nonshivering thermogenesis in anesthetized humans. *ANESTHESIOLOGY* 1993; 79:695-703
74. Plattner O, Semsroth M, Sessler DI, Papoušek A, Klasek C, Wagner O: Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. *ANESTHESIOLOGY* 1997; 86:772-7
75. Giesbrecht GG, Sessler DI, Mekjavic IB, Schroeder M, Bristow GW: Treatment of immersion hypothermia by direct body-to-body contact. *J Appl Physiol* 1994; 76:2373-9
76. Horvath SM, Spurr GB, Hutt BK, Hamilton LH: Metabolic cost of shivering. *J Appl Physiol* 1956; 8:595-602
77. Israel DJ, Pozos RS: Synchronized slow-amplitude modulations in the electromyograms of shivering muscles. *J Appl Physiol* 1989; 66:2358-63
78. Sessler DI, Rubinstein EH, Moayeri A: Physiologic responses to mild peri-anesthetic hypothermia in humans. *ANESTHESIOLOGY* 1991; 75:594-610
79. Hammel HT, Hardy JD, Fusco MM: Thermoregulatory responses to hypothalamic cooling in unanesthetized dogs. *Am J Physiol* 1960; 198:481-6
80. Kanosue K, Zhang Y-H, Yanase-Fujiwara M, Hosono T: Hypothalamic network for thermoregulatory shivering. *Am J Physiol* 1994; 267:R275-82
81. Birzis L, Hemingway A: Efferent brain discharge during shivering. *J Neurophysiol* 1957; 20:156-66
82. Gilbert TM, Blatteis CM: Hypothalamic thermoregulatory pathways in the rat. *J Appl Physiol* 1977; 43:770-7
83. Stuart DG, Kawamura Y, Hemingway A: Activation and suppression of shivering during septal and hypothalamic stimulation. *Exp Neurol* 1961; 4:485-506
84. Stuart DG, Kawamura Y, Hemingway A: Effects of septal and hypothalamic lesions on shivering. *Exp Neurol* 1962; 5:335-47
85. Halvorson I, Thornhill J: Posterior hypothalamic stimulation of anesthetized normothermic and hypothermic rats evokes shivering thermogenesis. *Brain Res* 1993; 610:208-15
86. Benzinger TH, Pratt AW, Kitzinger C: The thermostatic control of human metabolic heat production. *Proc Natl Acad Sci U S A* 1961; 47:730-9
87. Asami A, Asami T, Hori T, Kiyohara T, Nakashima T: Thermally-induced activities of the mesencephalic reticulospinal and rubrospinal neurons in the rat. *Brain Res Bull* 1988; 20:387-98
88. Henneman E: Organization of the motoneuron pool: The size principle, *Medical Physiology*, 14th Edition. Edited by Mountcastle VB. St. Louis, CV Mosby, 1980, pp 718-41
89. Stuart D, Ott K, Ishikawa K, Eldred E: The rhythm of shivering: I. General sensory contributions. *Am J Physic Med* 1966; 45:61-74
90. Stuart D, Ott K, Ishikawa K, Eldred E: The rhythm of shivering: II. Passive proprioceptive contributions. *Am J Physic Med* 1966; 45:75-90
91. Stuart D, Ott K, Ishikawa K, Eldred E: The rhythm of shivering: III. Central contributions. *Am J Physic Med* 1966; 45:91-104
92. Stelter WJ, Klussmann FW: [Influence of spinal cord temperature on the stretch response of tonic and phasic alpha-motoneurons]. *Pflügers Arch* 1969; 309:310-27
93. Henneman E, Somjen G, Carpenter DO: Excitability and inhibibility of motoneurons of different sizes. *J Neurophysiol* 1965; 28:599-620
94. Klussmann FW, Spaan G, Stelter HJ, Rau B: Synchronization of motor neuron discharges during shivering (letter). *Pflügers Arch* 1969; 312:R108
95. Lupandin I: [Regulation of the function of gamma- and alpha-motor neurons of antagonist muscles during cold tremor in the cat]. *Neurofiziologija* 1983; 15:242-8
96. Niemann U, Windhorst U, Meyer-Lohmann J: Linear and nonlinear effects in the interactions of motor units and muscle spindle afferents. *Exp Brain Res* 1986; 63:639-49
97. Lippold OCJ, Redfearn JWT, Vuco J: The influence of afferent and descending pathways on the rhythmical and arrhythmical components of muscular activity in man and the anaesthetized cat. *J Physiol* 1959; 146:1-9
98. Günther H, Brunner R, Klussmann FW: Spectral analysis of tremorine and cold tremor electromyograms in animal species of different size. *Pflügers Arch* 1983; 399:180-5
99. Schäfer SS, Schäfer S: The behavior of the proprioceptors of the muscle and the innervation of the fusimotor system during cold shivering. *Exp Brain Res* 1973; 17:364-80
100. Schäfer SS, Schäfer S: The role of the primary afference in the generation of a cold shivering tremor. *Exp Brain Res* 1973; 17:381-93
101. Meurer KA, Jessen C, Iriki M: [Cold-shivering during isolated cooling of the spinal cord following section of the dorsal roots]. *Pflügers Arch* 1967; 293:236-55
102. De Courcy JG, Eldred C: Artefactual "hypotension" from shivering. *Anaesthesia* 1989; 44:787-8
103. Barker SJ, Shah NK: Effects of motion on the performance of pulse oximeters in volunteers. *ANESTHESIOLOGY* 1996; 85:774-81
104. Mahajan RP, Grover VK, Sharma SL, Singh H: Intraocular pressure changes during muscular hyperactivity after general anesthesia. *ANESTHESIOLOGY* 1987; 66:419-21
105. Rosa G, Pinto G, Orsi P, De Blasi RA, Conti G, Sanita R, La Rosa I, Gasparetto A: Control of post anaesthetic shivering with nefopam hydrochloride in mildly hypothermic patients after neurosurgery. *Acta Anaesthesiol Scand* 1995; 39:90-5
106. Ostheimer GW, Datta S: Observations in the postpartum recovery room after various local anesthetic techniques. *Reg Anesth* 1981; 6:13-7
107. Ciofolo MJ, Clergue F, Devilliers C, Ben-Ammar M, Viars P: Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. *ANESTHESIOLOGY* 1989; 70:737-41
108. Just B, Delva E, Camus Y, Lienhart A: Oxygen uptake during recovery following naloxone. *ANESTHESIOLOGY* 1992; 76:60-4
109. Frank SM, Fleisher LA, Olson KE, Gorman RB, Higgins MS, Breslow MJ, Sitzmann JV, Beattie C: Multivariate determinants of early postoperative oxygen consumption in elderly patients. *ANESTHESIOLOGY* 1995; 83:241-9
110. Carli F, Gabrielczyk M, Clark MM, Aber VR: An investigation of factors affecting postoperative rewarming of adult patients. *Anaesthesia* 1986; 41:363-9
111. Collins KJ, Dore C, Exton-Smith AN, Fox RH, MacDonald IC, Woodward PM: Accidental hypothermia and impaired temperature homeostasis in the elderly. *BMJ* 1977; 1:353-6
112. Vassilief N, Rosencher N, Sessler DI, Conseiller C: The shivering threshold during spinal anesthesia is reduced in the elderly. *ANESTHESIOLOGY* 1995; 83:1162-6
113. Kurz A, Plattner O, Sessler DI, Huemer G, Redl G, Lackner F: The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than young patients. *ANESTHESIOLOGY* 1993; 79:465-9
114. Ozaki M, Sessler DI, Suzuki H, Ozaki K, Atarashi K, Negishi C: The threshold for thermoregulatory vasoconstriction during nitrous oxide/sevoflurane anesthesia is reduced in elderly patients. *Anesth Analg* 1997; 84:1029-33
115. Collins KJ, Exton-Smith AN, Dore C: Urban hypothermia: preferred temperature and thermal perception in old age. *BMJ* 1981; 282:175-7
116. Wagner JA, Robinson S, Marino RP: Age and temperature regulation of humans in neutral and cold environments. *J Appl Physiol* 1974; 37:562-5
117. Stoner HB, Frayn KN, Little RA, Threlfall CJ, Yates DW, Barton RN, Heath DF: Metabolic aspects of hypothermia in the elderly. *Clin Sci* 1980; 59:19-27
118. Gautier H, Bonora M, Schultz SA, Remmers JE: Hypoxia-induced changes in shivering and body temperature. *J Appl Physiol* 1987; 62:2477-84
119. Iwashita H, Matsukawa T, Ozaki M, Sessler DI, Imamura M, Kumazawa T: Hypoxemia decreases the shivering threshold in rabbits anesthetized with 0.2 MAC isoflurane. *Anesth Analg* 1998; 87:1408-11
120. Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzmann JV, Raff H, Beattie C: The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. *ANESTHESIOLOGY* 1995; 82:83-93
121. Hines R, Barash PG, Watrous G, O'Connor T: Complications occurring in the postanesthesia care unit: A survey. *Anesth Analg* 1992; 74:503-9
122. Vaughan MS, Vaughan RW, Cork RC: Postoperative hypothermia in adults: Relationship of age, anesthesia, and shivering to rewarming. *Anesth Analg* 1981; 60:746-51
123. Holm EP, Sessler DI, Standl T, am Esch JS: Shivering following normothermic desflurane or isoflurane anesthesia. *Acta Anaesthesiol Scand Suppl* 1997; 111:321-2

124. Horn E-P, Sessler DI, Standl T, Schroeder F, Bartz H-J, Beyer J-C, Schulte am Esch J: Non-thermoregulatory shivering in patients recovering from isoflurane or desflurane anesthesia. *ANESTHESIOLOGY* 1998; 89:878-86
125. Horn E-P, Schroeder F, Wilhelm S, Sessler DI, Standl T, von dem Busche K, Schulte am Esch J: Postoperative pain facilitates non-thermoregulatory tremor. *ANESTHESIOLOGY* 1999; 91:979-84
126. Panzer O, Ghazanfari N, Sessler DI, Yücel Y, Greher M, Akca O, Donner A, Germann P, Kurz A: Shivering and shivering-like tremor during labor with and without epidural analgesia. *ANESTHESIOLOGY* 1999; 90:1609-16
127. Lenhardt R, Negishi C, Sessler DI, Ozaki M, Tayefeh F, Kurz A: Paralysis only slightly reduces the febrile response to interleukin-2 during isoflurane anesthesia. *ANESTHESIOLOGY* 1998; 89:648-56
128. Frank SM, Kluger MJ, Kunkel SL: Elevated thermosensitive setpoint in post-operative patients. *ANESTHESIOLOGY* 2000; 93:1426-31
129. Hynson JM, Sessler DI, Glosten B, McGuire J: Thermal balance and tremor patterns during epidural anesthesia. *ANESTHESIOLOGY* 1991; 74:680-90
130. Rosner G: The influence of thermal stimulation of the spinal cord and skin on the activity of hypothalamic units. *J Comp Physiol* 1978; 126:151-6
131. Boulant JA, Bignall KE: Changes in thermosensitive characteristics of hypothalamic units over time. *Am J Physiol* 1973; 225:311-8
132. Parmeggiani PL, Cevolani D, Azzaroni A, Ferrari G: Thermosensitivity of anterior hypothalamic-preoptic neurons during the waking-sleeping cycle: a study in brain functional states. *Brain Res* 1987; 415:79-89
133. Hori T, Shibata M, Kiyohara T, Nakashima T: Prefrontal cortical influences on behavioural thermoregulation and thermosensitive neurons. *J Therm Biol* 1984; 9:27-31
134. Shibata M, Hori T, Kiyohara T, Nakashima T: Activity of hypothalamic thermosensitive neurons during cortical spreading depression in the rat. *Brain Res* 1984; 308:255-62
135. Hori T, Kiyohara T, Nakashima T, Shibata M: Responses of preoptic thermosensitive neurons to medial forebrain bundle stimulation. *Brain Res Bull* 1982; 8:667-75
136. Berner NJ, Heller HC: Does the preoptic anterior hypothalamus receive thermoafferent information? *Am J Physiol* 1998; 274: R9-18
137. Grahn DA, Heller HC: Activity of most rostral ventromedial medulla neurons reflect EEG/EMG pattern changes. *Am J Physiol* 1989; 257:R1496-505
138. Grahn DA, Radeke CM, Heller HC: Arousal state vs. temperature effects on neuronal activity in subcoeruleus area. *Am J Physiol* 1989; 256:R840-9
139. Richard G, Johnstone M: The effect of methylphenidate (ritalin) on post-halothane muscular spasticity. *Br J Anaesth* 1970; 42:718-21
140. Vogelsang J, Hayes SR: Stadol [butorphanol] attenuates postanesthesia shivering. *J Post Anesth Nursing* 1989; 4:222-7
141. Joris J, Banache M, Bonnet F, Sessler DI, Lamy M: Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *ANESTHESIOLOGY* 1993; 79:532-9
142. Sarma V, Fry ENS: Doxapram after general anaesthesia: Its role in stopping shivering during recovery. *Anaesthesia* 1991; 46:460-1
143. Sharma DR, Thakur JR: Ketamine and shivering. *Anaesthesia* 1990; 45: 252-3
144. Horn EP, Standl T, Sessler DI, von Knobelsdorff G, Büchs C, Schulte am Esch J: Physostigmine prevents postanesthetic shivering as does meperidine or clonidine. *ANESTHESIOLOGY* 1998; 88:108-13
145. Kurz M, Belani K, Sessler DI, Kurz A, Larson M, Blanchard D, Schroeder M: Naloxone, meperidine, and shivering. *ANESTHESIOLOGY* 1993; 79:1193-201
146. De Witte JL, Kim J-S, Sessler DI, Bastanmehr H, Bjorksten AR: Tramadol reduces the shivering, vasoconstriction, and sweating thresholds. *Anesth Analg* 1998; 87:173-9
147. Kizilirmak S, Karakas SE, Akça O, Özkan T, Yavru A, Pembeci K, Sessler DI, Telci L: Magnesium sulfate stops postanesthetic shivering. *Ann N Y Acad Sci* 1997; 813:799-806
148. Fry ENS: Postoperative shivering (letter). *Anaesthesia* 1983; 38:172
149. Greif R, Rajek A, Laciny S, Doufas AG, Sessler DI: Neither nalbuphine, a kappa-receptor opioid, nor atropine possesses special anti-shivering activity (abstract). *Eur J Anaesthesiol* 1999; 17(Suppl 19):A-273
150. Pauca AL, Savage RT, Simpson S, Roy RC: Effect of pethidine, fentanyl and morphine on post-operative shivering in man. *Acta Anaesthesiol Scand* 1984; 28:138-43
151. Nalda MA, Gomar C, Luis M: The effect of ketanserin on post-anaesthetic vasoconstriction and shivering. *Eur J Anaesthesiol* 1985; 2:265-77
152. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C: Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1997; 87:835-41
153. Götz E, Bogosyan S, Müller E, Litz R: [Treatment of postoperative shivering with nalbuphine]. *Anaesthesiol Intensivmed Notfallmed Schmerzther* 1995; 30:28-31
154. Powell RM, Buggy DJ: Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. *Anesth Analg* 2000; 90:1423-7
155. Rodriguez JL, Weissman C, Damask MC, Askanazi J, Hyman AI, Kinney JM: Physiologic requirements during rewarming: Suppression of the shivering response. *Crit Care Med* 1983; 11:490-7
156. Zwischenberger JB, Kirsh MM, Dechert RE, Arnold DK, Bartlett RH: Suppression of shivering decreases oxygen consumption and improves hemodynamic stability during postoperative rewarming. *Ann Thorac Surg* 1987; 43: 428-31
157. Feldberg W, Myers RD: A new concept of temperature regulation by amines in the hypothalamus (letter). *Nature* 1963; 200:1325
158. Feldberg W, Myers RD: Effects on temperature of amines injected into the cerebral ventricles: A new concept of temperature regulation. *J Physiol* 1964; 173:226-37
159. Hellon RF: Monoamines, pyrogens and cations: Their actions on central control of body temperature. *Pharmacol Rev* 1975; 26:289-321
160. Gordon CJ: *Temperature Regulation in Laboratory Rodents*. Cambridge, Cambridge University Press, 1993
161. Myers RD, Lee TF: Neurochemical aspects of thermoregulation. *Advances in Comparative and Environmental Physiology*. Edited by Wang LCH. Berlin, Springer Verlag, 1989, pp 161-203
162. Myers RD, Yaksh TL: Feeding and temperature responses in the unrestrained rat after injections of cholinergic and aminergic substances into the cerebral ventricles. *Physiol Behav* 1968; 3:917-28
163. Quan N, Blatteis CM: Intracerebrally microdialyzed and microinjected norepinephrine evokes different thermal responses. *Am J Physiol* 1989; 257: R816-21
164. Findlay JD, Thompson GE: The effect of intraventricular injections of noradrenaline, 5-hydroxytryptamine, acetylcholine and tranlycpromine on the ox (*Bos taurus*) at different environmental temperature. *J Physiol* 1968; 194: 809-16
165. Bligh J, Cottle WH, Maskrey M: Influence of ambient temperature responses to 5-hydroxytryptamine, noradrenaline and acetylcholine injected into the lateral cerebral ventricles of sheep, goats and rabbits. *J Physiol* 1971; 212: 377-92
166. Myers RD: Hypothalamic control of thermoregulation. *Handbook of the Hypothalamus*. Edited by Morgane PJ, Panksepp J. New York, Marcel Dekker, 1980, pp 83-210
167. Zeisberger E: Biogenic amines and thermoregulatory changes. *Prog Brain Res* 1998; 115:159-76
168. Zeisberger E: Cold adaptation, Physiology and Pathophysiology of Temperature Regulation. Edited by Blatteis CM. Singapore, World Scientific, 1998, pp 208-27
169. Quan N, Xin L, Ungar AL, Blatteis CM: Preoptic norepinephrine-induced hypothermia is mediated by  $\alpha$ 2-adrenoceptors. *Am J Physiol* 1992; 262:R407-11
170. Myers RD, Chinn C: Evoked release of hypothalamic norepinephrine during thermoregulation in the cat. *Am J Physiol* 1973; 224:230-6
171. Ruwe WD, Ferguson AV, Baue L, Veale WL: Release of hypothalamic neurotransmitters: Alterations caused by exposure to a unique early thermal environment. *Thermal Physiology*. Edited by Hales JRS. New York, Raven, 1984, pp 129-32
172. Komiskey HL, Rudy TA: Serotonergic influences on brain stem thermoregulatory mechanisms in the cat. *Brain Res* 1977; 134:297-315
173. Watanabe T, Morimoto A, Murakami N: Effect of amine on temperature-responsive neuron in slice preparation of rat brain stem. *Am J Physiol* 1986; 250:R553-9
174. Zeisberger E, Ewen K: Ontogenetic, thermoadaptive and pharmacological changes in threshold and slope for thermoregulatory reactions in the guinea-pig (*Cavia aperea porcellus*). *J Therm Biol* 1983; 8:55-7
175. Brück K: Basic mechanisms in thermal long-term and short-term adaptations. *J Therm Biol* 1986; 11:73-7
176. Myers RD, Yaksh TL: Control of body temperature in the unanesthetized monkey by cholinergic and aminergic systems in the hypothalamus. *J Physiol* 1969; 202:483-500
177. Sweatman P, Jell RM: Dopamine and histamine sensitivity of rostral hypothalamic neurones in the cat: Possible involvement in thermoregulation. *Brain Res* 1977; 127:173-8
178. Scott IM, Boulant JA: Dopamine effects on thermosensitive neurons in hypothalamic tissue slices. *Brain Res* 1984; 306:157-63
179. Ruwe WD, Myers RD: Dopamine in the hypothalamus of the cat: Pharmacological characterization and push-pull perfusion analysis of sites mediating hypothermia. *Pharmacol Biochem Behav* 1978; 9:65-80
180. De Roij TA, Ferns J, Bakker J, Nemeth F: Thermoregulatory effects of intraventricularly injected dopamine in the goat. *Eur J Pharmacol* 1977; 43:1-7
181. Brown SJ, Gisolfi CV, Mora F: Temperature regulation and dopaminergic systems in the brain: Does the substantia nigra play a role? *Brain Res* 1982; 234:275-86
182. Green MD, Cox B, Lomax P: Sites and mechanisms of actions of histamine in the central thermoregulatory pathways of the rat. *Neuropharmacology* 1976; 15:321-4
183. Pilc A, Nowak JZ: The influence of 4-methylhistamine, an agonist of histamine H2 receptors on body temperature in rats. *Neuropharmacology* 1980; 19:773-5
184. Bugajski J, Zacny E: The role of central histamine H1- and H2-receptors in hypothermia induced by histamine in the rat. *Agents Actions* 1981; 11:442-7
185. Lomax P, Green MD: Histaminergic neurons in the hypothalamic thermoregulatory pathways. *FASEB J* 1981; 40:2741-5
186. Jasinski DR, Preston KL: A comparative assay of nefopam, morphine and d-amphetamine. *Psychopharmacology* 1987; 91:273-8

187. Tresnak-Rustad NJ, Wood ME: In vitro biochemical effects of nefopam hydrochloride, a new analgesic agent. *Biochem Pharmacol* 1981; 20:2847-50
188. Campos VM, Solis EL: The analgesic and hypothermic effects of nefopam, morphine, aspirin, diphenhydramine, and placebo. *J Clin Pharmacol* 1980; 20:42-9
189. Lehmann KA, Horrichs G, Hoeckle W: Tramadol as an intraoperative analgesic: A randomized double blind study with placebo. *Anaesthetist* 1985; 34:11-9
190. Pang WW, Huang PY, Chang DP, Huang MH: The peripheral analgesic effect of tramadol in reducing propofol injection pain: A comparison with lidocaine. *Reg Anesth Pain Med* 1999; 24:246-9
191. Driessen B, Reimann W: Interaction of the central analgesic tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. *Br J Pharmacol* 1992; 105:147-51
192. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL: Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an "atypical" opioid analgesic. *J Pharmacol Exp Ther* 1992; 260:275-85
193. Frink MC, Hennies HH, Englberger W, Haurand M, Wilffert B: Influence of tramadol on neurotransmitter systems of the rat brain. *Arzneimittelforschung* 1996; 46:1029-36
194. Lai J, Ma SW, Porreca F, Raffa RB: Tramadol, M1 metabolite and enantiomer affinities for cloned human opioid receptors expressed in transfected HN9.10 neuroblastoma cells. *Eur J Pharmacol* 1996; 316:369-72
195. Desmeules JA, Piguet V, Collart L, Dayer P: Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol* 1996; 41:7-12
196. Krause T, Tonner PH, Scholz J, Schweers S, Schulte am Esch J: Interaction of tramadol with cerebral alpha-2-adrenoceptors: Possible role in attenuation of postoperative shivering (abstract). *ANESTHESIOLOGY* 1999; 91:A-388
197. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *ANESTHESIOLOGY* 1991; 74:581-605
198. Surprenant A, North RA: Mechanism of synaptic inhibition by noradrenaline acting at  $\alpha$ -2-adrenoceptors. *Proc R Soc Biol* 1988; 234:85-114
199. Evans RJ, Surprenant A: Effects of phospholipase A2 inhibitors on coupling of  $\alpha$ -2-adrenoceptors to inwardly rectifying potassium currents in guinea pig submucosal neurones. *Br J Pharmacol* 1993; 10:591-6
200. Maze M: Clinical uses of alpha-2 agonists, 46th Annual Refresher Course Lectures. Atlanta, American Society of Anesthesiologists, 1995, p 125
201. Lipscombe D, Kongsamut S, Tsien RW:  $\alpha$ -adrenergic inhibition of sympathetic neurotransmitter release mediated by modulation of N-type calcium-channel gating. *Nature* 1989; 340:639-42
202. Myers RD, Simpson CW, Higgins D, Nattermann RA, Rice JC, Redgrave P, Metcalf G: Hypothalamic Na<sup>+</sup> and Ca<sup>++</sup> ions and temperature set-point: New mechanisms of action of a central or peripheral thermal challenge and intrahypothalamic 5-HT, NE, PGE1, and pyrogen. *Brain Res Bull* 1976; 1:301-27
203. Crisinel D, Bissonnette B, Feihl F, Gardaz JP: [Efficacy of ketanserin on postanesthetic shivering]. *Ann Fr Anesth Réanim* 1997; 16:120-5
204. Leysen JE, Niemegeers CJE, van Nueten JM, Laduron PM: [3H] Ketanserin (R41 468), a selective 3H-ligand for serotonin<sub>2</sub> receptor binding sites. *Mol Pharmacol* 1982; 21:301-14
205. Dewar KM, Lima L, Reader TA: [3H] ketanserin binds to non-5-HT<sub>2</sub> sites in rabbit cerebral cortex and neostriatum. *Neurochem Res* 1990; 15:507-14
206. Alhaider AA: Antinociceptive effect of ketanserin in mice: involvement of supraspinal 5-HT<sub>2</sub> receptors in nociceptive transmission. *Brain Res* 1991; 543:335-40
207. McCall RB, Schuette MR: Evidence for an alpha-1 receptor-mediated central sympathoinhibitory action of ketanserin. *J Pharmacol Exp Ther* 1984; 228:704-10
208. Koss MC: Mechanism of ketanserin-induced sympatho-inhibition. *Eur J Pharmacol* 1991; 194:161-6
209. Bock M, Sinner B, Göttlicher M, Martin E, Motsch J: Dolasetron prevents postanesthetic shivering (abstract). *ANESTHESIOLOGY* 1999; 91:A-1184
210. Mazzola-Pomietto P, Aulakh CS, Murphy DL: Temperature, food intake, and locomotor activity effects of a 5-HT<sub>3</sub> receptor agonist and two 5-HT<sub>3</sub> receptor antagonists in rats. *Psychopharmacology* 1995; 121:488-93
211. Sevcik J, Nieber K, Driessen B, Illes P: Effects of the central analgesic tramadol and its main metabolite, O-desmethyltramadol, on rat locus coeruleus neurones. *Br J Pharmacol* 1993; 110:169-76
212. Stamford JA: Descending control of pain. *Br J Anaesth* 1995; 75:217-27
213. Ruiz Ortega JA, Ugedo L: Activation of 5-HT<sub>1A</sub> receptors potentiates the clonidine inhibitory effect in the locus coeruleus. *Eur J Pharmacol* 1997; 333:159-62
214. Bamigbade TA, Davidson C, Langford RM, Stamford JA: Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus. *Br J Anaesth* 1997; 79:352-6
215. Hinckel P, Cristante L, Brück K: Inhibitory effects of the lower brain stem on shivering. *J Therm Biol* 1983; 8:129-31
216. Jones SL, Light AR: Serotonergic medullary raphespinal projection to the lumbar spinal cord in the rat: A retrograde immunohistochemical study. *J Comp Neurol* 1992; 322:599-610
217. Guyenet PG, Stornetta RL, Riley T, Norton FR, Rosin DL, Lynch KR: Alpha-2-adrenergic receptors are present in lower brainstem catecholaminergic and serotonergic neurons innervating spinal cord. *Brain Res* 1994; 638:285-94
218. Brück K, Hinckel P: Thermoafferent networks and their adaptive modifications, Thermoregulation: Physiology and Biochemistry. Edited by Schönbaum E, Lomax P. New York, Pergamon Press, 1990, pp 129-52
219. LaMotte CC, De Lanerolle NC: Ultrastructure of chemically defined neuron systems in the dorsal horn of the monkey. III. Serotonin immunoreactivity. *Brain Res* 1983; 274:65-77
220. Basbaum AI, Fields HL: Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci* 1984; 7:309-38
221. Spray DC: Cutaneous temperature receptors. *Annu Rev Physiol* 1986; 48:625-38
222. Anderson EG, Proudfit HK: The functional role of the bulbospinal serotonergic nervous system, Serotonin Neurotransmission and Behavior. Edited by Jacobs BL, Gelperin A. London, MIT Press, 1981, pp 307-38
223. Parry O, Roberts MHT: The responses of motoneurons to 5-hydroxytryptamine. *Neuropharmacology* 1980; 19:515-8
224. White SR, Neuman RS: Facilitation of spinal motoneuron excitability by 5-hydroxytryptamine and noradrenaline. *Brain Res* 1980; 188:119-27
225. Svensson TH, Bunney BS, Aghajanian GK: Inhibition of both noradrenergic and serotonergic neurons in brain by the  $\alpha$ -2-adrenergic agonist clonidine. *Brain Res* 1975; 92:291-306
226. Alojado MES, Ohta Y, Kemmotsu O: The effect of clonidine on the activity of neurons in the rat dorsal raphe nucleus in vitro. *Anesth Analg* 1994; 79:257-60
227. Guo TZ, Jiang JY, Buttermann AE, Maze M: Dexmedetomidine injection into the locus coeruleus produces antinociception. *ANESTHESIOLOGY* 1996; 84:873-81
228. Xie CW, Tang J, Han JS: Clonidine stimulated the release of dynorphin in the spinal cord of the rat: A possible mechanism for its depressor effects. *Neurosci Lett* 1986; 65:224-8
229. Klimscha W, Tong C, Eisenach JC: Intrathecal  $\alpha$ -2-adrenergic agonists stimulate acetylcholine and norepinephrine release from the spinal cord dorsal horn in sheep. *ANESTHESIOLOGY* 1997; 87:110-6
230. Botticelli LJ, Cox BM, Goldstein A: Immunoreactive dynorphin in mammalian spinal cord and dorsal root ganglia. *Proc Natl Acad Sci U S A* 1981; 78:7783-6
231. Myers RD, Beleslin DB, Rezvani AH: Hypothermia: role of alpha 1- and alpha 2-noradrenergic receptors in the hypothalamus of the cat. *Pharmacol Biochem Behav* 1987; 26:373-9
232. Jell RM: Responses of hypothalamic neurones to local temperature and to acetylcholine, noradrenaline and 5-hydroxytryptamine. *Brain Res* 1973; 55:123-34
233. Beckman AL, Eisenman JS: Microelectrophoresis of biogenic amines on hypothalamic thermosensitive cells. *Science* 1970; 170:334-6
234. Hall GH, Myers MD: Temperature changes produced by nicotine injected into the hypothalamus of the conscious monkey. *Brain Res* 1972; 37:241-51
235. Preston E: Central effects of cholinergic-receptor blocking drugs on the conscious rabbit's thermoregulation against body cooling. *J Pharmacol Exp Ther* 1974; 188:400-9
236. Kirkpatrick WE, Lomax P: The effect of atropine on the body temperature of the rat following systemic and intracerebral injection. *Life Sci* 1967; 6:2273-8
237. Mott JC: Effects of baroreceptor and chemoreceptor stimulation on shivering. *J Physiol (Lond)* 1963; 166:563-86
238. Myers RD, Waller MB: Differential release of acetylcholine from the hypothalamus and mesencephalon of the monkey during thermoregulation. *J Physiol* 1973; 230:273-93
239. Saxena AK, Tangri KK, Mishra N, Vrat S, Bhargava KP: Presence of cholinceptors in mesencephalic raphe nuclei concerned in thermoregulation in rabbits. *Clin Exp Pharmacol Physiol* 1984; 11:105-10
240. Griffiths EC, Slater P, Widdowson PS: The hypothermic action of carbachol in the rat brain periaqueductal grey area may involve neurotensin. *Br J Pharmacol* 1986; 1986:653-8
241. Romono JA, Shih TM: Cholinergic mechanisms of analgesia produced by physostigmine, morphine and cold water swimming. *Neuropharmacology* 1988; 22:827-33
242. Aiello-Malmberg P, Bartolini A, Bartolini R, Galli A: Effects of morphine, physostigmine and raphe nuclei stimulation on 5-hydroxytryptamine release from the cerebral cortex of the cat. *Br J Pharmacol* 1979; 65:547-55
243. Raskind MA, Peskind ER, Veith RC, Wilkinson CW, Federighi D, Dorsa DM: Differential effects of aging on neuroendocrine responses to physostigmine in normal men. *J Clin Endocrinol Metab* 1990; 70:1420-5
244. Pedigo NW, Dewey WL: Comparison of the antinociceptive activity of intravenicularly administered acetylcholine to narcotic antinociception. *Neurosci Lett* 1981; 26:85-90
245. Naguib M, Yaksh TL: Antinociceptive effects of spinal cholinesterase inhibition and isobolographic analysis of the interaction with  $\mu$  and  $\alpha$ 2 receptor systems. *ANESTHESIOLOGY* 1994; 80:1338-48
246. Baxendale BR, Mahajan RP, Crossley AW: Anticholinergic premedication influences the incidence of postoperative shivering. *Br J Anaesth* 1994; 72:291-4
247. Durieux ME: Muscarinic signaling in the central nervous system. *ANESTHESIOLOGY* 1996; 84:173-89



248. Záborszky L, Cullinan WE, Luine VN: Catecholamine-cholinergic interaction in the basal forebrain. *Prog Brain Res* 1993; 98:31-49
249. Semba K: Aminergic and cholinergic afferents to REM sleep induction regions of the pontine reticular formation in the rat. *J Comp Neurol* 1993; 330:543-56
250. Losier BJ, Semba K: Dual projections of single cholinergic and aminergic brainstem neurons to the thalamus and basal forebrain in the rat. *Brain Res* 1993; 604:41-52
251. Clark WG, Lipton JM: Brain and pituitary peptides in thermoregulation, Thermoregulation: Pathology, Pharmacology and Therapy. Edited by Schönbaum E, Lomax P. New York, Pergamon Press, 1991, pp 509-60
252. Saltzman SK, Beckman A: Effects of thyrotropin releasing hormone on hypothalamic thermosensitive neurons of the rat. *Brain Res Bull* 1981; 7:325-32
253. Hori T, Yamasaki M, Asami T, Koga H, Kiyohara T: Responses of anterior hypothalamic-preoptic thermosensitive neurons to TRH and Cyclo (His-Pro). *Neuropharmacology* 1988; 27:895-901
254. Kiyohara T, Hori T, Shibata M, Nakashima T: Effects of angiotensin II on preoptic thermosensitive neurons in the rat. *Thermal Physiology*. Edited by Hales JRS. New York, Raven Press, 1984, pp 141-4
255. Baldino Jr F, Beckman AL, Adler MW: Actions of iontophoretically applied morphine on hypothalamic thermosensitive units. *Brain Res* 1980; 196:199-208
256. Hori T, Yamasaki M, Kiyohara T, Shibata M: Responses of preoptic thermosensitive neurons to poikilothermia-inducing peptides-bombesin and neurotensin. *Pflügers Arch* 1986; 407:558-60
257. Cooper KE, Kasting NW, Lederis K, Veale WL: Evidence supporting a role for endogenous vasopressin in natural suppression of fever in the sheep. *J Physiol* 1979; 295:33-45
258. Kandasamy SB, Williams BA: Hypothermic and antipyretic effects of ACTH (1-24) and alpha-melanotropin in guinea-pigs. *Neuropharmacology* 1984; 23:49-53
259. Burks TF: Opioids and opioid receptors in thermoregulation, Thermoregulation: Pathology, Pharmacology and Therapy. Edited by Schönbaum E, Lomax P. New York, Pergamon Press, 1991, pp 489-508
260. Clark WG, Lipton JM: Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics and related agents. *Neurosci Biobehav Rev* 1985; 9:299-371
261. Bläsing J, Bäuerle U, Herz A: Endorphin-induced hyperthermia: characterization of the exogenously and endogenously induced effects. *Naunyn-Schmiedeberg's Arch Pharmacol* 1979; 309:137-43
262. Bloom AS, Tseng LF: Effects of beta-endorphin on body temperature in mice at different ambient temperatures. *Peptides* 1981; 2:293-7
263. Martin GE, Bacino CB: Action of intracerebrally injected beta-endorphin on the rat's core temperature. *Eur J Pharmacol* 1979; 59:227-36
264. Jacquet YF: Opposite temporal changes after a single central administration of beta-endorphin: Tolerance and sensitization. *Life Sci* 1982; 30:2215-9
265. Stanton TL, Sartin NF, Beckman AL: Changes in body temperature and metabolic rate following microinjection of Met-enkephalinamide in the preoptic/anterior hypothalamus of rats. *Regul Pept* 1985; 12:333-43
266. Lin MT, Chern YF, Chen FF, Su CY: Serotonergic mechanisms of beta-endorphin-induced hyperthermia in rats. *Pflügers Arch* 1979; 382:87-90
267. Liem ST, Aldrete JA: Control of post-anaesthetic shivering. *Can Anaesth Soc J* 1974; 21:506-10
268. Liu WHD, Luxton MC: Effect of prophylactic fentanyl on shivering in elective caesarean section under epidural analgesia. *Anaesthesia* 1991; 46:344-8
269. Shehabi Y, Gatt S, Buckman T, Isert P: Effect of adrenaline, fentanyl and warming of injectate on shivering following extradural analgesia in labour. *Anaesth Intens Care* 1990; 18:31-7
270. Lyons B, Carroll M, McDonald NJ: The treatment of postanesthetic shivering: A double blind comparison between alfentanil and pethidine. *Acta Anaesthesiol Scand* 1995; 39:979-82
271. Sevarino FB, Johnson MD, Lema MJ, Datta S, Ostheimer GW, Naulty JS: The effect of epidural sufentanil on shivering and body temperature in the parturient. *Anesth Analg* 1989; 68:530-3
272. Wheelahan JM, Leslie K, Silbert BS: Epidural fentanyl reduces the shivering threshold during epidural lidocaine anesthesia. *Anesth Analg* 1998; 87:587-90
273. Way WL, Way EL: Opioid Analgesics & Antagonists, Basic and Clinical Pharmacology, Third Edition. Edited by Katzung BG. Norwalk, Appleton & Lange, 1987, pp 336-49
274. Wrench JJ, Cavill G, Ward JEH, Crossley AWA: Comparison between alfentanil, pethidine and placebo in the treatment of post-anesthetic shivering. *Br J Anaesth* 1997; 79:541-2
275. Burks L, Aisner J, Fortner CL, Wiernik PH: Meperidine for the treatment of shaking chills and fever. *Arch Intern Med* 1980; 140:483-4
276. Guffin A, Girard D, Kaplan JA: Shivering following cardiac surgery: Hemodynamic changes and reversal. *J Cardiothorac Vasc Anesth* 1987; 1:24-8
277. Macintyre PE, Pavlin EG, Dwersteg JF: Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in post-anesthesia shivering. *Anesth Analg* 1987; 66:751-5
278. Alfonsi P, Sessler DI, Du Manoir B, Levron J-C, Le Moing J-P, Chauvin M: The effects of meperidine and sufentanil on the shivering threshold in postoperative patients. *ANESTHESIOLOGY* 1998; 89:43-8
279. Kurz A, Ikeda T, Sessler DI, Larson M, Bjorksten AR, Dechert M, Christensen R: Meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold. *ANESTHESIOLOGY* 1997; 86:1046-54
280. Kurz A, Sessler DI, Annadata R, Dechert M, Christensen R: Midazolam minimally impairs thermoregulatory control. *Anesth Analg* 1995; 81:393-8
281. Wang JJ, Ho ST, Lee SC, Liu YC: A comparison among nalbuphine, meperidine, and placebo for treating postanesthetic shivering. *Anesth Analg* 1999; 88:686-9
282. Horan PJ, Ho IK: Comparative pharmacological and biochemical studies between butorphanol and morphine. *Pharmacol Biochem Behav* 1989; 34:847-54
283. Pick CG, Paul D, Pasternak GW: Nalbuphine, a mixed kappa 1 and kappa 3 analgesic in mice. *J Pharmacol Exp Ther* 1992; 262:1044-50
284. Wongchanapai W, Tsang BK, He Z, Ho IK: Differential involvement of opioid receptors in intrathecal butorphanol-induced analgesia compared to morphine. *Pharmacol Biochem Behav* 1998; 59:723-7
285. Yakimova KS, Sann H, Pierau FK: Effects of kappa and delta opioid agonists on activity and thermosensitivity of rat hypothalamic neurons. *Brain Res* 1998; 786:133-42
286. Alojado MES, Ohta Y, Yamamura T, Kimmotsu O: The effect of fentanyl and morphine on neurons in the dorsal raphe nucleus in the rat: An in vitro study. *Anesth Analg* 1994; 78:726-32
287. Ohta Y, Alojado MES, Kimmotsu O: Activity changes in rat raphe magnus neurons at different concentrations of fentanyl in vitro. *Anesth Analg* 1995; 80:890-5
288. Fu MJ, Tsen LY, Lee TY, Lui PW, Chan SH: Involvement of cerulospinal glutamatergic neurotransmission in fentanyl-induced muscular rigidity in the rat. *ANESTHESIOLOGY* 1997; 87:1450-9
289. Harrison C, Smart D, Lambert DG: Stimulatory effects of opioids. *Br J Anaesth* 1998; 81:20-8
290. Boulant JA: Hypothalamic neurons: Mechanisms of sensitivity to temperature. *Ann N Y Acad Sci* 1998; 856:108-15
291. Griffin JD, Kaple ML, Chow AR, Boulant JA: Cellular mechanisms for neuronal thermosensitivity in the rat hypothalamus. *J Physiol* 1996; 492:231-42
292. McFadzean I, Lacey M, Hill R, Henderson G: Kappa opioid receptor activation depresses excitatory synaptic input to rat locus coeruleus neurons in vitro. *Neuroscience* 1987; 20:231-9
293. Dickenson AH: Spinal cord pharmacology of pain. *Br J Anaesth* 1995; 75:193-200
294. Myers RD, Yaksh TL: Thermoregulation around a new "set-point" established in the monkey by altering the ratio of sodium to calcium ions within the hypothalamus. *J Physiol* 1971; 218:609-33
295. Myers RD, Veale WL: The role of sodium and calcium ions in the hypothalamus in the control of body temperature of the unanaesthetized cat. *J Physiol* 1971; 212:411-30
296. Myers RD, Tytell M: Fever: Reciprocal shift in brain sodium to calcium ratio as the setpoint temperature rises. *Science* 1972; 178:765-7
297. Myers RD: Diencephalic efflux of  $^{22}\text{Na}^+$  and  $^{45}\text{Ca}^{2+}$  ions in the febrile cat: Effect of an antipyretic. *Brain Res* 1976; 103:412-7
298. Lynch CI: Voltage-gated calcium channels, Anesthesia: Biologic Foundations. Edited by Yaksh TL, Lynch CI, Zapol WM, Maze M, Biebuyck JF, Saidman LJ. Philadelphia, Lippincott-Raven, 1998, pp 163-96
299. Seoane JR, Baile CA: Feeding and temperature changes in sheep following injections of barbiturates,  $\text{Ca}^{++}$ , or  $\text{Mg}^{++}$  into the lateral, third, or fourth ventricle or cerebral aqueduct. *J Dairy Sci* 1975; 58:515-20
300. Myers RD: The role of ions in thermoregulation and fever, Pyretics and Antipyretics. Edited by Milton AS. Berlin, Springer, 1982, pp 151-86
301. Neubeiser RE, Platner WS, Shields JL: Magnesium in blood and tissues during cold exposure. *J Appl Physiol* 1961; 16:247-9
302. Stendig-Lindberg G, Moran D, Shapiro Y: How significant is magnesium in thermoregulation? *J Basic Clin Physiol Pharmacol* 1998; 9:73-85
303. Parsons MT, Owens CA, Spellacy WN: Thermic effects of tocolytic agents: Decreased temperature with magnesium sulfate. *Obstet Gynecol* 1987; 69:88-90
304. Reynolds JEF: Martindale: The Extra Pharmacopoeia, 29th Edition. London, Pharmaceutical Press, 1989, p 1896
305. Kornhuber J, Parsons CG, Hartmann S, Retz W, Kamolz S, Thome J, Riederer P: Orphenadrine is an uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist: Binding and patch clamp studies. *J Neural Transm Gen Sect* 1995; 102:237-46
306. Fry ENS: Postoperative analgesia using papaveretum and orphenadrine. *Anaesthesia* 1979; 34:281-3
307. Yamamura T, Harada K, Okamura A, Kimmotsu O: Is the site of action of ketamine anesthesia the *N*-methyl-D-aspartate receptor? *ANESTHESIOLOGY* 1990; 72:704-10
308. White PF, Way WL, Trevor AJ: Ketamine: Its pharmacological and therapeutic uses. *ANESTHESIOLOGY* 1982; 56:119-36
309. Hirota K, Lambert DG: Ketamine: Its mechanism(s) of action and unusual clinical uses (editorial). *Br J Anaesth* 1996; 77:441-4
310. Lundy PM, Lockwood PA, Thompson G, Frew R: Differential effects of ketamine isomers on neuronal and extraneuronal catecholamine uptake mechanisms. *ANESTHESIOLOGY* 1986; 64:359-63

311. Crisp T, Perrotti JM, Smith DL, Stafinsky JL, Smith DJ: The local monoaminergic dependency of spinal ketamine. *Eur J Pharmacol* 1991; 194:167-72
312. Taylor DCM, Gayton RJ, Miley HE, Cross NP, Parton MP: The effects of *N*-methyl-D-aspartate (NMDA) and non-NMDA receptor agonists and antagonists on hypothalamic neurones in the anaesthetized rat which respond to changes in scrotal skin temperature. *Neurosci Lett* 1995; 201:259-61
313. Van Gaalen M, Kawahara H, Kawahara Y, Westerink BH: The locus coeruleus noradrenergic system in the rat brain studied by dual-probe microdialysis. *Brain Res* 1997; 763:56-62
314. Singewald N, Kaehler ST, Hemeida R, Philippu A: Influence of excitatory amino acids on basal and sensory stimuli-induced release of 5-HT in the locus coeruleus. *Br J Pharmacol* 1998; 123:746-52
315. Dodson ME, Fryer JM: Postoperative effects of methylphenidate. *Br J Anaesth* 1980; 52:1265-70
316. Taylor D, Ho BT: Comparison of inhibition of monoamine uptake by cocaine, methylphenidate and amphetamine. *Res Commun Chem Pathol Pharmacol* 1978; 21:67-75
317. Dalal S, Melzack R: Potentiation of opioid analgesia by psychostimulant drugs: A review. *J Pain Symptom Manage* 1998; 16:245-53
318. Janowsky AJ, Hauger RL: CNS Stimulants, Principles of Pharmacology: Basic Concepts and Clinical Applications. Edited by Munson PL. New York, Chapman & Hall, 1995, pp 453-64
319. Bamford OS, Dawes GS, Hanson MA, Ward RA: The effects of doxapram on breathing, heart rate and blood pressure in fetal lambs. *Respir Physiol* 1986; 66:387-96
320. Riddell PL, Robertson GS: Use of doxapram as an arousal agent in outpatient general anaesthesia. *Br J Anaesth* 1978; 50:921-4
321. Kesecioglu J, Rupprecht J, Telci L, Dzoljic M, Erdmann W: Effect of aminophylline or physostigmine on recovery from nitrous oxide-enflurane anaesthesia. *Acta Anaesthesiol Scand* 1991; 35:616-20
322. Roy RC, Stulken EH: Electroencephalographic evidence of arousal in dogs from halothane after doxapram, physostigmine, or naloxone. *ANESTHESIOLOGY* 1981; 55:392-7
323. Kee N: Intrathecal pethidine: Pharmacology and clinical applications. *Anaesth Intensive Care* 1998; 26:137-46
324. Alfonsi P, Hongnat JM, Lebraut C, Chauvin M: The effects of pethidine, fentanyl and lignocaine on postanesthetic shivering. *Anaesthesia* 1995; 50:214-7
325. Glosten B, Sessler DI, Ostman LG, Faure EAM, Thisted RA: Intravenous lidocaine does not cause tremor or alter thermoregulation. *Reg Anesth* 1991; 16:218-22
326. Carlsson A, Lindqvist M: Central and peripheral monoaminergic membrane-pump blockade by some addictive analgesics and antihistamines. *J Pharm Pharmacol* 1969; 21:460-4
327. Rogers KJ: Role of brain monoamines in the interaction between pethidine and tranylcypromine. *Eur J Pharmacol* 1971; 14:86-8
328. Larsen JJ, Hyttel J: 5-HT-uptake inhibition potentiates antinociception induced by morphine, pethidine, methadone and ketobemidone in rats. *Acta Pharmacol et Toxicol* 1985; 57:214-8
329. Carmichael EJ, Israel Y: In vitro inhibitory effects of narcotic analgesics and other psychotropic drugs on the active uptake of norepinephrine in mouse brain tissue. *J Pharmacol Exp Ther* 1973; 186:253-60
330. Montel H, Starke K, Weber F: Influence of fentanyl, levorphanol and pethidine on the release of noradrenaline from rat brain cortex slices. *Naunyn Schmiedeberg Arch Pharmacol* 1974; 283:371-7
331. Montel H, Starke K: Effects of narcotic analgesics and their antagonists on the rabbit isolated heart and its adrenergic nerves. *Br J Pharmacol* 1973; 49:628-41
332. Izenwasser S, Newman AH, Cox BM, Katz JL: The cocaine-like behavioral effects of meperidine are mediated by activity at the dopamine transporter. *Eur J Pharmacol* 1996; 297:9-17
333. Ebert B, Andersen S, Krogsgaard-Larsen P: Ketobemidone, methadone and pethidine are non-competitive *N*-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett* 1995; 187:165-8
334. Jones BW: The use of Demerol as an anesthetic agent. *J Am Assoc Nurse Anesth* 1974; 42:439-46
335. Hustveit O, Setekleiv J: Fentanyl and pethidine are antagonists on muscarinic receptors in guinea-pig ileum. *Acta Anaesthesiol Scand* 1993; 37:541-4
336. Takada K, Tonner PH, Maze M: Meperidine functions as an alpha2B adrenoceptor agonist (abstract). *ANESTHESIOLOGY* 1999; 91:A-809
337. Sessler DI: A proposal for new temperature monitoring and thermal management guidelines (letter). *ANESTHESIOLOGY* 1998; 89:1298-300
338. Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST: Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997; 336:540-6
339. Churn SB, Taft WC, Billingsley MS, Blair RE, DeLorenzo RJ: Temperature modulation of ischemic neuronal death and inhibition of calcium/calmodulin-dependent protein kinase II in gerbils. *Stroke* 1990; 21:1715-21
340. Dietrich WD, Busto R, Halley M, Valdes I: The importance of brain temperature in alterations of the blood-brain barrier following cerebral ischemia. *J Neuropathol Exp Neurol* 1990; 49:486-97
341. Minamisawa H, Smith M-L, Siesjo BK: The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. *Ann Neurol* 1990; 28:26-33
342. Vacanti RX, Ames A III: Mild hypothermia and Mg<sup>++</sup> protect against irreversible damage during CNS ischemia. *Stroke* 1984; 15:695-8
343. Anonymous: Perioperative shivering. *Lancet* 1991; 338:547-8
344. Grundy HF: Cardiovascular effects of morphine, pethidine, diamorphine and nalorphine on the cat and rabbit. *Br J Pharmacol* 1971; 42:159-78
345. Muldoon SM, McKenzie JE, Collins FJ: Pressor effect of nalbuphine in hemorrhagic shock is dependent on the sympathoadrenal system. *Circ Shock* 1988; 26:89-98
346. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J: Tramadol: Pain relief by an opioid without depression of respiration. *Anaesthesia* 1992; 47:291-6
347. Heel RC, Brogden RN, Pakes GE, Speight TM, Avery GS: Nefopam: A review of its pharmacological properties and therapeutic efficacy. *Drugs* 1980; 19:249-67
348. Schaffer K, Braun HA: Modulation of cutaneous cold receptor function by electrolytes, hormones and thermal adaptation. *Physiol Res* 1992; 41:71-5
349. Kozyreva TV: Two periods in the response of the skin cold receptors to intravenous infusion of noradrenaline. *Ann N Y Acad Sci* 1997; 813:176-83
350. Panksepp J: Hypothalamic integration of behaviour: Rewards, punishments, and related psychological processes, *Handbook of the Hypothalamus*. Edited by Morgane PJ, Panksepp J. New York, 1980, pp 289-431
351. Nieuwenhuys R: "New" entities in the central nervous system: The [paracrine?] core and its adjuncts, *Chemoarchitecture of the Brain*. Berlin, Springer-Verlag, 1985, pp 177-93
352. Gebhart GF, Sandkuhler J, Thalhammer JG, Zimmermann M: Inhibition of spinal nociceptive information by stimulation in midbrain of the cat is blocked by lidocaine microinjected in nucleus raphe magnus and medullary reticular formation. *J Neurophysiol* 1983; 50:1446-59
353. Széleányi Z, Hinckel P: Changes in cold- and heat-defence following electrolytic lesions of raphe nuclei in the guinea-pig. *Pflügers Arch* 1987; 409:175-81