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The dorsomedial hypothalamus: a new player in thermoregulation

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DMicco, Joseph A., and Dmitry V. Zaretsky. The dorsomedial hypothalamus: a new player in thermoregulation. Am J Physiol Regul Integr Comp Physiol 292: R47–R63, 2007. First published September 7, 2006; doi:10.1152/ajpregu.00498.2006.—Neurons in the dorsomedial hypothalamus (DMH) play key roles in physiological responses to exteroceptive (“emotional”) stress in rats, including tachycardia. Tachycardia evoked from the DMH or seen in experimental stress in rats is blocked by microinjection of the GABA_A receptor agonist muscimol into the rostral raphe pallidus (rRP), an important thermoregulatory site in the brain stem, where disinhibition elicits sympathetically mediated activation of brown adipose tissue (BAT) and cutaneous vasoconstriction in the tail. Disinhibition of neurons in the DMH also elevates core temperature in conscious rats and sympathetic activity to least significant difference interscapular BAT (IBAT) and BAT temperature in anesthetized preparations. The latter effects are blocked by microinjection of muscimol into the rRP, while microinjection of muscimol into either the rRP or DMH suppresses increases in sympathetic nerve activity to IBAT, IBAT temperature, and core body temperature elicited either by microinjection of PGE_2 into the preoptic area (an experimental model for fever), or central administration of fentanyl. Neurons concentrated in the dorsal region of the DMH project directly to the rRP, a location corresponding to that of neurons transsynaptically labeled from IBAT. Thus these neurons control nonshivering thermogenesis in rats, and their activation signals its recruitment in diverse experimental paradigms. Evidence also points to a role for neurons in the DMH in thermoregulatory cutaneous vasoconstriction, shivering, and endocrine adjustments. These directions provide intriguing avenues for future exploration that may expand our understanding of the DMH as an important hypothalamic site for the integration of autonomic, endocrine, and behavioral responses to diverse challenges.

brown fat; sympathetic nervous system; body temperature; fever; raphe pallidus

THERMOREGULATION IN MAMMALS is a vital process orchestrated by the central nervous system through endocrine, autonomic, and behavioral mechanisms. One of the first regions of the brain to be linked with this process was the preoptic area (POA), an area that is not only the location of temperature sensitive neurons but receives and integrates input from ascending neural pathways carrying information derived from sensory receptors in the periphery (for reviews see refs. 21, 80, 112). The result is a coordinated array of adaptive changes that involve multiple systems and are aimed at maintaining and stabilizing body temperature. Although the POA plays a similar role in virtually all mammals, the specific means through which normothermia is attained may vary in different species. In rats, normothermia in a cold environment is maintained in part through metabolic activation of brown adipose tissue (BAT) (105; for a review, see Ref. 27), a tissue whose existence and significance in adult humans has been the subject recently of considerable controversy and interest (see also Ref. 7), and cutaneous vasoconstriction, a mechanism used by both these species, as well as other mammals. These effects that serve to generate body heat and regulate heat loss, respectively, are sympathetically mediated and accompanied by adrenergic cardiac stimulation (35, 63, 125, 194), which is thought to aid in the distribution of heat generated in thermogenic regions (i.e., brown fat) and by contraction in skeletal muscle (i.e., shivering). In addition to these sympathetic actions that could be viewed as constituting rapid adjustments, exposure to cold results also in characteristic endocrine effects in mammals. These include alterations of thyroid function (15, 61) and activation of the hypothalamo-pituitary-adrenal axis to increase circulating glucocorticoids (106, 153, 190, 206), actions, which together promote an array of metabolic effects in support of the increased thermogenic needs of the organism. Finally, somatic motor nerves promote the generation of heat by skeletal muscle through shivering (23, 39, 180, 190).

Over the past half century, a number of brain regions have been implicated in the circuitry downstream from the POA that...
might be involved in these various components of the system outlined above. In recent years, the dorsomedial hypothalamus (DMH) has rapidly emerged as an area of considerable interest with regard to certain of these thermoregulatory mechanisms. In this review, we summarize the evidence in support of a role for the DMH in thermoregulation and dysregulation in mammals, principally, with respect to thermoregulatory mechanisms that are sympathetically mediated. However, we will also briefly consider evidence that dimly, but intriguingly, illuminates the possibility of a role for neurons in the same region in thermoregulatory adjustments that involve endocrine and somatomotor effects. As we will use the term, the thermoregulatory DMH indicates a region of the hypothalamus that includes the dorsomedial hypothalamic nucleus (DMN) but also extends into adjoining areas, particularly dorsal and perhaps posterior to the nucleus itself, as defined in the current standard atlas (154). Indeed, as we will suggest below, the specific neurons that may be relevant to thermoregulation probably do not correspond precisely to any of the classically delineated hypothalamic nuclei or regions.

Search for a Hypothalamic “Thermogenic Center”

Three decades ago, the notion of a hypothalamic region distinct from the POA had not been integrated into the “black box” model of the brain in thermoregulation (see Refs. 24 and 75). Nevertheless, it soon became clear that additional components linking temperature-sensitive neurons in the POA to appropriate effector outputs were needed to provide a cogent operational framework. The first hypothalamic region to receive serious consideration in this regard was the ventromedial hypothalamus (VMH). Electrical stimulation of the VMH was found to elicit increased norepinephrine turnover and thermogenesis in IBAT (79, 88, 95, 157, 171, 215) and to increase markedly and specifically blood flow in this tissue (90). Conversely, electrolytic lesion of the VMH abolished cold-induced increases in sympathetic nerve activity to IBAT (142), while microinjection of the local anesthetic lidocaine into the region of the VMH reduced the increase in IBAT temperature evoked by cooling or stimulation of the POA (90). Within this body of literature, the hypothesis that the VMH comprises a second hypothalamic “thermogenic center” seems to have been established by earlier reports, and this notion clearly influenced the interpretation of the results of many of the studies that followed. For example, when electrical stimulation of either the VMH or the DMH was found to elevate IBAT temperature, attention was focused on the VMH, nonetheless (95). Similarly, Thornhill and colleagues (204) found that microinjection of lidocaine into either the VMH or the nearby posterior hypothalamus (PH) reduced the increase in IBAT temperature evoked from the POA in anesthetized rats, calling into question the relevant site of action for the microinjected agent, and neither report using lidocaine in this manner addressed the potential for affecting fibers of passage with this approach. Furthermore, the increases in IBAT temperature that were produced by electrical stimulation of the VMH in many of these studies were typically preceded by small, but consistent, decreases, a fact that seems to have been often, but not always (see Refs. 212 and 213) ignored. The biphasic nature of the temperature response in this study, as well as the failure of electrical stimulation of the VMH to evoke any increase in IBAT temperature in a later report (62), precludes a clear interpretation of the data. Indeed, a thorough understanding of precisely which neural elements are activated by intracerebral electrical stimulation, as well as the exact mechanism for this activation, has proven elusive for decades (see Ref. 158). This and the possibility of effects resulting from spread or diffusion of microinjected drugs to adjacent regions (see below) undermine the rationale for this earlier conclusion that activation of neurons in the VMH results in nonshivering thermogenesis.

In spite of the uncertainty regarding the interpretation of the results of electrically stimulating and lesioning specific sites in the brain, experiments using these approaches provided the first indication that neurons in the DMH might play a role in thermoregulation. Historically, the DMH had been implicated in feeding and metabolic regulation associated with ingestive behavior (for a review, see Ref. 12), phenomena closely linked to thermoregulation for decades (70, 105, 169). Consequently, the finding that IBAT weight was significantly reduced in rats with lesions of the DMH (13) was interpreted only in this context. In fact, increases in BAT mass are known to reflect thermogenic accommodation to a cold environment that is sympathetically mediated (133, 164). A more direct link between the DMH and thermogenesis in BAT was posed by studies in which electrical stimulation of the VMH had no effect on IBAT temperature, while stimulation of the DMH (as well as several other hypothalamic regions) increased it (62). Active sites of stimulation seemed to represent a continuous band extending caudally from the preoptic area through the anterior hypothalamus, hypothalamic paraventricular nucleus (PVN) and DMH. Consequently, the authors surmised that observed thermogenic effects resulted from activation of fibers of passage emanating caudally from the preoptic area. (Cursory, however, they suggested that this pathway was inhibitory to brain stem thermogenic mechanisms, a conclusion seemingly at odds with their results.)

The potential for stimulation of fibers of passage was, in fact, largely responsible for the abandonment of electrical stimulation in favor of chemical stimulation, generally achieved by local microinjection of highly concentrated solutions of glutamate or other excitatory amino acids (68). Studies using this approach reported that microinjection of glutamate into either the VMH, the PVN, or the PH—regions virtually surrounding the DMH—increased IBAT temperature in anesthetized rats (2–4, 71). Amir (4) also reported that similar microinjection of the GABA<sub>A</sub> receptor antagonist bicuculline methiodide (BMI) 50 ng, or ∼100 pmol, into the PH increased core and IBAT temperature. Assuming that the results of these studies represent actions of glutamate or BMI on neurons as opposed to fibers of passage, they clearly suggested that activation of hypothalamic neurons located outside of the preoptic area could elicit sympathetically mediated activation of BAT. However, without appropriate anatomic controls and given the ambiguity regarding the exact delineation of PH vs. DMH (see below and Ref. 184), the precise location of the relevant neurons remained unclear. Even less illuminating were the results of Yoshimatsu and colleagues (219), who studied the effects of microinjections of glutamate into several hypothalamic regions on sympathetic nerve activity to IBAT in anesthetized rats. They reported a confusing array of stimulatory, inhibitory, and biphasic responses, and that the predominant response evoked from the DMH was inhibitory, a finding
that appears contradictory in light of more recent results detailed below. An explanation may lie in the fact that microinjection of highly concentrated solutions of excitatory amino acids to excite local neurons may have just the opposite effect (111), probably owing to depolarizing blockade. Accordingly, microinjection of NMDA into the DMH at doses in the range of 0.68 to 6.8 pmol evokes marked dose-related tachycardia in anesthetized rats, but doses only slightly higher (20 pmol) produce a lower response, and doses higher still (60 pmol) had little or no effect on heart rate (184). Thus the relevant sympahtoexcitatory neurons in the DMH may be unusually sensitive to glutamate receptor agonists so that microinjection of excitatory amino acids at the millimolar concentrations typically used fail to evoke increased activity (see also ref. 49).

Therefore, studies using the technique of microinjection of glutamate did little to clarify the specific location of the hypothalamic neurons controlling sympathetic activity to BAT or to suggest that DMH might be a prime candidate in this regard. However, microinjection of calcitonin gene-related peptide (CGRP) into the either the DMH or the VMH in urethane-anesthetized rats evoked sharp increases in IBAT and core body temperature, oxygen consumption, and heart rate (101). The authors demonstrated a degree of anatomical specificity for the effect—similar injections into the POA or the PVN were ineffective—but failed to resolve the region further or to pursue the suggestion that the DMH might represent a hypothalamic thermogenic region of some significance. Instead, the bias toward a focus on the VMH is evident in both the design of their studies, the results selected for representation, and the tenor of the discussion in this work. Nevertheless, the DMH was now added to the list of hypothalamic regions that might represent upstream sites involved in the control of nonshivering thermogenesis in rats (135).

**DMH Emerges as a Key Hypothalamic Sympahtoexcitatory Region**

The search for the precise location of one or more hypothalamic sympathetic thermogenic areas was thus set against the backdrop of a confusing array of data, suggesting a wide number of possibilities that principally included the PVN, the PH, and the VMH. As indicated above, however, these three areas together bracket and surround the DMH, a region that by the end of the last century had emerged as a major integrative site for the classic defense reaction and responses to experimental exteroceptive stress (for a review, see Ref. 50). Thus, in conscious rats, disinhibition of neurons in the DMH by local microinjection of BMI—at doses less than one-tenth of the dose used by Amir (4) to evoke thermogenesis in the PH—evokes an array of autonomic, behavioral, and endocrine response, typically seen in stress, among these being marked sympathetically mediated tachycardia (9, 45, 184). Conversely, local microinjection of muscimol, an inhibitor of the vast majority of mammalian neurons by virtue of its agonist properties at GABA_A receptors, virtually abolished the sympathetically mediated increases in heart rate seen in experimental air jet stress (191, 192).

Most importantly, the brain stem pathway mediating DMH-evoked cardiac stimulation was subsequently found to involve the region of the rostral raphe pallidus (rRP) in the medulla (172), a discovery that provided the first strong indication of a role for the DMH in thermoregulation. The rRP, a midline longitudinal region at the base of the medulla between the pyramids, as well as the adjacent parapyramidal area and perhaps raphe magnus, was revealed to be an important location of sympathetic premotor neurons in circuits innervating BAT and thermoregulatory cutaneous blood vessels from the results of transsynaptic neuronal tracing studies (for a review of the technique, see Refs. 10, 29, 137, 183, 186). Moreover, functional studies had clearly demonstrated that activation—or disinhibition—of neurons in the rRP by local microinjection of BMI resulted in dramatic increases in sympathetic nerve activity to IBAT and increases in IBAT temperature and metabolism, as well as in anesthetized rats (128, 129, 132). However, it was also noted that these effects were accompanied by tachycardia and modest increases in blood pressure (132), replicating the pattern of cardiovascular changes evoked by activation of the DMH or by stress in this species.

Subsequent studies provided support for the notion that key sympahtoexcitatory effects of activating neurons in the DMH were in fact mediated through neuronal activity in the rRP and that a direct projection from neurons in the former region to the latter might be involved. The sympathetically mediated tachycardia that could be evoked by microinjection of BMI into the DMH was mimicked by similar disinhibition of neurons in the rRP (30, 166) and was suppressed by 30–60% after microinjection of muscimol into the latter region (30, 81, 172). Furthermore, specific sites in the DMH shown to be most sensitive to the tachycardic effects of “nanoinjectons” of BMI at a reduced dose (2 pmol) and volume (5 nl) corresponded closely to the area where neurons projecting to the rRP were most highly concentrated (173; see Fig. 1). Thus sympathetically mediated tachycardia seen in stress may be mediated, at least in part, through excitatory projections from the DMH to the rRP, a pathway originating principally from a dense collection of neurons in the dorsal area of the former region that had already been well described and characterized anatomically (85–87). However, given the recent elucidation of the rRP as a key medullary site for sympathetic control of BAT and cutaneous vasoconstriction, these findings also suggested that neurons in the DMH might constitute the hypothalamic thermoregulatory site whose existence had been suggested more than two decades earlier.

**DMH and Thermoregulatory Mechanisms: Sympahtic Activation of Brown Fat**

Zaretskaia and colleagues (221) provided the first clear evidence that activation of neurons in the DMH could dramatically alter body temperature through a classic thermoregulatory mechanism. They demonstrated that, in addition to autonomic, endocrine, and behavioral effects already described, microinjection of BMI into the DMH markedly elevated core body temperature in conscious freely moving rats at room temperature (Fig. 2). In urethane-anesthetized rats, similar microinjections evoked rapid and dramatic increases in IBAT temperature that preceded and exceeded the responses in core temperature (Fig. 3), suggesting that the former was at least partly responsible for the latter. Most importantly, a dose of 10 pmol of BMI in 100 nl was used—one-tenth the dose and less than half the volume injected by Amir and colleagues into the PH as discussed above—and identical microinjections into the
VMH or the PVN failed to affect either core or IBAT temperature. Thus inclusion of the appropriate anatomical control data that were missing from earlier studies ruled out the possibility that the effects noted may have been a consequence of spread or diffusion of BMI to either region.

Subsequently, Cao and colleagues (31) performed detailed experiments in anesthetized animals that confirmed and extended these findings by characterizing further the thermogenic response to disinhibition of the DMH and establishing the role of the rRP in these changes. Microinjection of BMI (60 pmol) into the DMH dramatically elevated IBAT, renal, and cardiac sympathetic nerve activity, as well as heart rate and blood pressure, and these elevations were associated with marked increases in IBAT temperature and expired CO₂, a reflection of increased metabolic activity in BAT and, perhaps, the heart as well (Fig. 4). DMH-evoked increases in IBAT temperature, IBAT sympathetic nerve activity, and metabolism were greatly attenuated or abolished by microinjection of muscimol into the rRP, implying that activation of sympathetic premotor neurons in the latter region played a dominant role in these changes. On the other hand, although peak increases in heart rate were significantly reduced, increases in renal or cardiac sympathetic nerve activity and in blood pressure were unaffected. The marked effect of microinjection of muscimol into the rRP on IBAT temperature and sympathetic nerve activity clearly points to a critical role for neuronal activity in the region in the thermogenic response.

More recently, Cao and Morrison have provided insight into the nature of the excitatory signaling through which disinhibition of neurons in the DMH activates thermogenic mechanisms in the rRP. In anesthetized rats, they explored the effect of microinjection of glutamate receptor antagonists into the rRP with respect to responses to microinjection of BMI into the DMH (33). Microinjection of kynurenate, a nonselective antagonist of all ionotropic glutamate receptors, rapidly (i.e., within 5 min of injection) and completely abolished BMI-induced increases in sympathetic nerve activity to IBAT and attenuated the accompanying increases in IBAT temperature without affecting increases in heart rate, arterial pressure, and renal sympathetic nerve activity. Injection of AP5 or of CNQX, antagonists with the capacity for relative selectivity against NMDA vs. non-NMDA subtypes of ionotropic glutamate receptors, respectively, elicited effects similar to those of kynurenate. These findings thus suggest that DMH-induced sympathetic activation of BAT is mediated at least, in part, through stimulation of ionotropic glutamate receptors in the rRP.

A close examination of the results of published anatomic tracing studies provides supporting evidence that neurons in the DMH are contributors to sympathetic activation of BAT and thus play a role in thermoregulation. Most relevant are those studies in which the transneuronal tracing technique based upon sequential transsynaptic infection by pseudorabies virus (PRV) was applied to elucidate central pathways projecting to IBAT, all of which reported labeling in the DMH (10, 29, 31, 137, 147, 217). In fact, the results shown in one such report indicate a particularly dense collection of PRV-infected neurons in the region of the DMH just dorsal to the DMN and thus play a role in thermoregulation. Most relevant are those studies in which the transneuronal tracing technique based upon sequential transsynaptic infection by pseudorabies virus (PRV) was applied to elucidate central pathways projecting to IBAT, all of which reported labeling in the DMH (10, 29, 31, 137, 147, 217). In fact, the results shown in one such report indicate a particularly dense collection of PRV-infected neurons in the region of the DMH just dorsal to the DMN and extending somewhat ventrally into the latter nucleus itself (217; Fig. 1). This distribution, suggested by the authors as being in the PH, closely matches that of neurons retrogradely labeled directly from the rRP, in what was previously identified as the dorsal hypothalamic area (77, 85, 143, 173), as well as that of sites most sensitive to the cardiac sympathoexcitatory effect of microinjected BMI (173; Fig. 1). Together, these results indicate that neurons that project directly to the rRP and
polysynaptically to IBAT are found in the same region of the DMH—a region to which various labels have been appended. Thus both anatomic and functional experiments support the existence of direct projections from the DMH to the rRP, the activation of which results in sympathetically mediated thermogenesis in BAT. Clearly, much of our knowledge regarding the role of the DMH in thermoregulation is framed in the functional context of these projections, and this notion has already served to illuminate new paths for exploration as detailed below. However, more recent studies suggest an alternative efferent pathway through which the DMH may exert significant thermogenic effects. Like neurons in the dorsal DMH, neurons in the caudal periaqueductal gray (cPAG) are retrogradely labeled from the rRP (77, 143), transsynaptically labeled from IBAT (10, 29, 217), and express fos after exposure to cold (29). Chen and coworkers (37) reported that electrical or chemical stimulation of neurons in this region increases IBAT temperature in anesthetized rats, suggesting that neurons in the cPAG are interposed in neural circuits that can stimulate the activity of BAT. De Menezes and colleagues (44) studied the effect of inhibiting neurons in the cPAG on responses evoked from the DMH in conscious rats. Microinjection of muscimol into the cPAG not only reduced the DMH-induced increases in heart rate and locomotor activity but also suppressed the associated increases in body temperature (Fig. 5). Although de Menezes and colleagues targeted a different subregion of the cPAG than did Chen and coworkers (36, 37) (i.e., the lateral/dorsolateral vs. the lateral/ventrolateral PAG), it seems likely that, given the anatomic resolution possible with the microinjection techniques used, the same neurons were involved in all effects described. Interestingly, neurons retrogradely labeled from the cPAG were found in the area of the dorsal DMH corresponding to that where rRP-projecting neurons are concentrated, and these same neurons were shown to express fos in response to exposure to a cold environment (10°C; 218). These results suggest that neurons in the same region of the DMH project to the rRP both directly and indirectly through a neuronal relay in the cPAG and that thermogenesis in BAT may be a consequence of activating either pathway. Whether the same hypothalamic neurons project to both downstream thermogenic regions is currently unknown.

Just as neurons in the DMH are positioned to signal sympathetic premotor neurons in the rRP that regulate the activity of BAT through these efferent pathways, they are also known to receive afferent input from regions that may be relevant to thermoregulation (for a review, see Ref. 202). Principal among these is the POA, a region of prime importance with regard to thermoregulation. In tracing studies, the POA has been identified as the region containing the largest number of neurons retrogradely labeled from the DMH (202). Many neurons in the POA are known to be GABAergic (146), and those that are relevant to thermoregulation are thought to exert tonic inhibition of downstream elements important for activation of BAT (36). As discussed above, microinjection of BMI, a GABA_A receptor antagonist, is an efficient means of evoking activation of neurons in the DMH that are involved in sympathetic control of IBAT, suggesting that these neurons are restrained by tonic GABAergic inhibition under normal circumstances. Recently, neurons in the DMH retrogradely labeled from the rRP were found to receive GABAergic projections originating in the POA (138). Thus GABAergic neurons in the POA are likely to provide a key source of the tonic inhibitory input to sympathoexcitatory neurons in the DMH that was first implied by experimental findings two decades ago (47).

**DMH and Thermoregulatory Mechanisms: Sympathetic Cutaneous Vasoconstriction**

The clear evidence that neuronal activation in the DMH elicits sympathetic thermogenesis through activation of BAT and that this effect is mediated through the medullary rRP invites the possibility that cutaneous vasoconstriction, the other major sympathetic thermoregulatory mechanism apparently controlled from this region, might also be under similar descending control from the DMH. Cutaneous vasoconstriction and vasodilation serve to conserve or dissipate body heat, respectively, and so represent important thermoregulatory adjustments in mammals. The particular cutaneous region principally involved in this function may vary according to species. In rabbits, the cutaneous circulation of the pinna is of primary
importance (98, 197), while in rats, blood flow to the tail serves this purpose (43, 74, 159, 193). As with sympathetic innervation of BAT, the rRP appears to represent the brain stem location of sympathetic premotor neurons that specifically regulate these anatomically distinct but functionally analogous circulations in these two species, i.e., the tail in rats (20, 137, 149, 151, 152, 160, 161, 183, 196) and the pinna in rabbits (17, 19, 140, 149, 150).

The hypothesis that neurons in the DMH play a role in thermoregulatory vasoconstriction mediated through the rRP has not been explicitly examined, but recent reports provide some supportive evidence. In a transsynaptic retrograde tracing study in rats, substantial labeling was consistently seen in the DMH—and more specifically in the dorsal hypothalamic area and, to a somewhat lesser degree, in the DMN—7 days after injection of pseudorabies virus into the wall of the rat tail artery (183). Electrical stimulation of the DMH was subsequently reported to decrease blood flow in the ear of anesthetized rabbits (97, 148). Nalivaiko and Blessing (139) found that electrical stimulation of the region of the DMH in anesthetized paralyzed rabbits reduced blood flow in the pinna by more than 80% but mesenteric blood flow was reduced only by 50%. More importantly, the reduction in blood flow to the ear induced by hypothalamic stimulation was completely abolished by prior injection of muscimol into the rRP, while the decrease in mesenteric blood flow was unaffected. This finding suggests that a pinna-specific vasoconstrictor pathway from the DMH to the rRP may exist in rabbits. However, the limitations regarding the interpretation of results from electrical stimulation studies discussed above make a connection with neurons in the DMH tenuous. Thus a likely possibility—and one ripe for investigation—is that, in rats, activation of neurons projecting from the DMH to the rRP elicits cutaneous vasoconstriction in the tail and that this pathway participates in thermoregulation.

DMH and Thermoregulatory Mechanisms: Beyond the Sympathetic Nervous System?

Although sympathetic innervation of brown fat and the cutaneous blood flow to the tail play a key role in rapid

![Image](https://example.com/image.png)

Fig. 3. Left: effect of unilateral microinjection of BMI 10 pmol/50 nl into the DMH (solid symbols), the paraventricular nucleus (PVN; open symbols), or the VMH (shaded symbols) on core (triangles) and interscapular brown adipose tissue (IBAT; squares) temperature, heart rate, and blood pressure in urethane-anesthetized rats. Right: schematic coronal sections representing two levels of the DMH and depicting eight of the injection sites in the DMH and all six injection sites into the VMH from the experiments at left. Solid circles denote an increase in both core and IBAT temperature accompanied by increases in heart rate of at least 40 beats/min; open circles denote no effect on temperature and increase in heart rate of less than 40 beats/min; open triangles denote no effect on temperature or heart rate. Numbers indicate distance from bregma in millimeters. [from Zaretskaia et al. (221)]
thermoregulatory responses in the rat, other systems are also involved in the maintenance of body temperature. This is particularly true in humans where, in adults, the significance of brown fat is currently a subject of some debate (see Refs. 7 and 27). What other systems, then, are considered “thermogenic” in our own species?

First, endocrine mechanisms are known to play at least a supporting metabolic role in thermoregulatory responses. These mechanisms include the adrenal cortex, where secretion of glucocorticoids has wide-ranging metabolic effects, and the thyroid gland, the hormones of which are thought to increase the metabolic rate in general and are specifically permissive for heat generation through the induction of uncoupling protein 1 in BAT and perhaps other tissues (15, 106, 108, 195). The activity of both glands is under central control by neurons that regulate the release of the pituitary trophic hormones ACTH and thyrotropin, respectively, and the final common pathway controlling their release is thought to be through neurons in the hypothalamic PVN (for reviews, see Refs. 58, 76, 175). The parvocellular PVN, the principal location of neurons that contain corticotrophin-releasing hormone and so control the secretion of ACTH, represents a principal hypothalamic target for efferent projections from the DMH in the rat (200, 201), and some of these projections are known to contact thyrotropin-releasing hormone-containing neurons in this region (121). Disinhibition of the DMH results in increased fos expression in the PVN and elevated plasma ACTH (9, 48, 221; see Fig. 2 of this article), whereas inhibition of neurons in the DMH suppresses the increases in plasma ACTH and in fos expression in the parvocellular PVN seen in experimental (air jet) stress in rats (127, 192). Thus the activation of the PVN that occurs in this stress paradigm appears to be signaled from neurons in the DMH. Accordingly, experimental stress increases fos expression in neurons in the DMH that are retrogradely labeled from the PVN (42, 110).

![Fig. 4. Effect of microinjection of muscimol into the rostral raphe pallidus (RPa) on responses evoked by microinjection of bicuculline (BIC) into the DMH in anesthetized rats. A: microinjection of bicuculline into DMH (dashed vertical line) elicits marked increases in IBAT sympathetic nerve activity (iBAT SNA) and temperature (BAT Temp), as well as expired CO₂ (Exp CO₂), reflecting increased metabolic activity, cardiac sympathetic nerve activity (iCSNA), heart rate (HR), renal sympathetic nerve activity (iRSNA), and mean arterial pressure (MAP) in a representative experiment. B: similar injection of BIC after microinjection of muscimol into the RPa in the same experiment fails to increase IBAT SNA or temperature or to increase expired CO₂, while the effects on cardiac indices are modestly reduced, and renal SNA and MAP are unaffected. C: Data from 4–9 experiments averaged over time. [from Cao et al. (31)]](http://ajpregu.physiology.org/doi/10.1152/ajpregu.00588.2006)
In addition to autonomic and endocrine mechanisms, humans and other mammals may also recruit the somatic motor outflow to generate heat through shivering. Neurons in the hypothalamus have been implicated in the generation of thermoregulatory shivering for decades (see Ref. 39), and earlier electrical stimulation studies suggested that shivering could be evoked from the VMH in conscious rabbits (126) and from the PH—but not the VMH—in anesthetized rats (72, 203). Other studies over the years have attempted to characterize the efferent pathway from the POA that mediates shivering using localized knife cuts and lesions (92, 93). Only recently, however, has clear evidence appeared that neuronal activity in a specific hypothalamic region downstream from the POA may play a role in shivering. In anesthetized rats, an electromyo-gram was recorded while body temperature was permitted to fall, and the resulting activity was usually (but not always) abolished by microinjection of muscimol into the DMH, the adjacent dorsal hypothalamus, and the dorsomedial region of the adjoining PH (195). Although a more precise location of the relevant neurons was unclear from the results presented, the reactive region clearly included the same area of the DA/DMH where putative thermoregulatory neurons projecting to the rRP and to the PAG are found. Even more recently, the increase in the activity of fusimotor fibers to the gastrocnemius elicited by cooling of the trunk skin in anesthetized rats—a response thought to be the mechanism responsible for thermoregulatory shivering—was blocked by microinjection of the inhibitory amino acid glycine into the rRP (197). This finding indicated that, in addition to its well-established role in sympathetic thermoregulatory mechanisms, neurons in the rRP may function in nonsympathetic thermoregulatory responses as well. That the same may be true of neurons in the DMH that project to the rRP has been recently suggested by the report of an intriguing neuroanatomic link between the DMH and somatomotor function. In a dual PRV transsynaptic tracing study from the adrenal gland, a sympathetic component well known to be activated in cold exposure (28, 46, 64, 84, 209), and the sympathectomized gastrocnemius muscle in rats, double-labeled neurons were evident in only a few brain regions, and, among these, were the DMH and cPAG (96). Thus neurons in the DMH that project to the rRP are appropriately interposed in anatomic circuits that could elicit shivering under appropriate conditions, making this another appealing area for further investigation.

Fig. 5. Effect of identical microinjection of BMI 10 pmol into the DMH on body temperature (TEMP) and heart rate (HR) after microinjection of either saline or muscimol (MUS) 100 pmol into ipsilateral sites in the caudal periaqueductal grey (cPAG; injection sites shown in schematics below) in the same conscious rats. *Significant differences between muscimol and saline treatments. d, dorsal; dl, dorsolateral; l, lateral; vl, ventrolateral. [from de Menezes et al. (44)]

Involvement of DMH in Physiological and Pathophysiological Thermoregulatory Phenomena: Cold Defense and Fever

Thus disinhibition of neurons in the region of the DMH results in increases in body temperature at least, in part, through 1) neuronal activity in the rRP and 2) sympathetically mediated activation of BAT. In the brief period since the recognition of a potential role for neurons in the DMH in the control of core body temperature, evidence has appeared for their participation in thermoregulatory responses in several different settings where activation of BAT and/or cutaneous vasoconstriction has been implicated.

One such circumstance is cold defense, or the recruitment of mechanisms that both generate and conserve body heat in a cold environment. In rats, these include activation of BAT and cutaneous vasoconstriction in the tail. Under such conditions, increased fos expression, and so presumably neuronal activation, has been reported in the DMH (8, 29, 119, 216). In urethane-anesthetized rats, intense fos expression was noted in the DMH of rats kept at an ambient temperature of 5°C but not at 23°C (119). In conscious cats, marked fos expression was also noted specifically in the dorsal DMH, the same region where neurons projecting to the rRP are known to be most densely concentrated, after exposure to either 10°C (97) or 5°C (216). Furthermore, the cold-induced fos expression in the DMH was dramatically suppressed by warming of the POA (216), an observation consistent with the idea that temperature-sensitive neurons in the POA exert tonic inhibitory control over thermoregulatory neurons in the DMH (see Ref. 138).
Although these results suggest that neurons in the DMH are activated in exposure to cold, no study to date has shown that this activation occurs specifically in neurons in the region that project to the rRP. However, Cano and coworkers (29) reported that in rats exposed to 4°C for 4 h, fos expression was clearly evident in the same region of the dorsal DMH, where neurons transsynaptically labeled from IBAT are concentrated (Fig. 1). Thus, not only are neurons that project directly to the rRP and polysynthetically to IBAT found in the same region of the DMH but neurons in this region appear to be activated in cold exposure. Because of this finding, Cano and coworkers (29) suggested that these neurons might play a key role in cold-induced thermogenesis. Evidence for their hypothesis has emerged in the preliminary finding of Almeida and colleagues that rats with electrolytic lesions of the DMH are unable to maintain normal body temperature in a cold environment (1). However, given that such lesions destroy local fibers of passage, as well as neurons, the hypothesis remains to be tested directly in appropriate functional studies.

Another setting in which evidence of a role for the recruitment of thermogenic mechanisms through activation of the DMH has now appeared is fever. Fever, a regulated increase in body temperature achieved by increasing the thermostatic set-point, is a salient component of a host response to bacterial infection that in mammals includes immunologic, autonomic, endocrine, and behavioral adjustments (for reviews, see Refs. 73, 102, 115, 176). In rats, sympathetic activation of BAT and endocrine, and behavioral adjustments (for reviews, see Refs. 16, 41, 53, 168). Consequently, systemic administration of LPS replicates many of the features of the acute phase response, including fever and so has become a widely employed experimental paradigm in rats. Another well-accepted model for fever based upon the mechanism proposed above is the central administration of PGE₂, which reliably and markedly increases body temperature in rats when given either by intracerebroventricular infusion or microinjected directly into the POA (5, 116, 127, 136, 144).

The results of experiments that used this latter experimental paradigm first suggested that the DMH might be involved in fever two decades ago. Zabawska and colleagues (220) attempted to localize the central site of a putative cholinergic link in the generation of hyperthermia elicited by microinjection of PGE₂ into the POA. In conscious control rats, rectal temperature was elevated by more than 1.5°C 15 min after microinjection of PGE₂, and this effect was essentially abolished after microinjection of atropine sulfate into either the dorsal or dorsomedial hypothalamus (fig. 6). The dose of atropine injected (5 μg, or ~7 nmol) was sufficiently high to call into question the pharmacological specificity of this effect, thus undermining the stated purpose of the study. Nevertheless, anatomic specificity was apparent since identical microinjections of atropine into the VMH or the thalamic dorsal to the DMH failed to influence PGE₂-induced hyperthermia.

In contrast to the experiments of Zabawska and colleagues, anatomic specificity appears to have been assumed in a subsequent study that used this same model for fever but focused on
the VMH (5). Here, microinjection of muscimol into the VMH was reported to reduce markedly the increase in both IBAT temperature and core temperature elicited by microinjection of PGE2 into the POA in anesthetized rats (5). However, in this case, the site of action was simply assumed to be the VMH, based upon the prevailing hypothesis that the VMH represented the primary hypothalamic site for sympathetic control of BAT. In retrospect, this assumption clearly was clearly ill conceived, especially given that the high dose of muscimol (440 pmol) and large volume of injection in which it was delivered (500 nl) made it highly likely that neurons in surrounding regions (such as the DMH) might be affected.

Thus, although the report of Zabawska and colleagues, a study that included appropriate anatomic control experiments, was the first to implicate neurons in the region of the DMH in experimental fever, the idea was forgotten, in deference to prevailing dogma until the more recent convergence of new lines of evidence outlined above. Specifically, microinjection of muscimol into the rRP was shown to block both the increases in core body temperature, IBAT temperature, and sympathetic nerve activity to IBAT caused by microinjection of PGE2 into the POA in anesthetized rats (130, 136). The latter observations clearly implicated activation of the thermoregulatory sympathetic premotor neurons in the rRP in this model of fever in rats. At the same time, a link had been forged between sympathoexcitatory neurons in the DMH and those in the rRP (172). Together, these findings brought the potential role of the DMH in fever into focus.

In studies that paralleled those of the rRP, microinjection of muscimol into the DMH was indeed shown to suppress the febrile response evoked by microinjection of PGE2 into the POA. Zaretskaia and colleagues (222) first showed that unilateral microinjection of muscimol into the DMH evoked an immediate suppression of the elevation in body temperature elicited by injection of PGE2 into the ipsilateral POA in anesthetized rats. At the same time, injection of muscimol produced a smaller, but significant, effect on the accompanying increase in heart rate. This result was subsequently confirmed in expanded studies by Madden and Morrison (116; fig. 7) and Nakamura and colleagues (138) who found that bilateral microinjections of muscimol into the DMH during the plateau phase of the febrile response rapidly reversed the PGE2-induced increases in IBAT sympathetic nerve activity, IBAT temperature, expired CO2, and heart rate. Most importantly, identical microinjection of muscimol into the lateral hypothalamus, another hypothalamic area where disinhibition has recently been shown to elicit thermogenesis (34), failed to influence any of the PGE2-induced increases (138). Thus a degree of anatomic specificity for the effect of microinjections into the DMH was clearly demonstrated. In one study, similar
microinjection of the ionotropic glutamate receptor antagonist kynurenic acid into the DMH also countered PGE2-induced changes. Thus, not only was neuronal excitation in the DMH largely responsible for the activation of BAT and other accompanying sympathetic effects elicited by PGE2 acting in the POA, but this excitation appeared to rely on activation of excitatory glutamate receptors in the region. The latter finding paralleled the results of Soltis and DiMicco more than a decade earlier, demonstrating a role for activation of ionotropic glutamate receptors in the DMH in stress-induced tachycardia (185), now also known to be mediated largely through the rRP (223).

These current findings invite a reappraisal of the results of prior studies aimed at elucidating the hypothalamic circuitry mediating the febrile response. Past results seemed to point to the classic suspects as “downstream” mediators of fever evoked from the POA, including the PVN (25, 83; also, see Ref. 57), the PH (123), and the VMH (124). In the case of each of these regions, the critical functional evidence supporting its role was that lesioning or inhibiting local neurons was reported to attenuate experimentally induced fever. However, as discussed above, once again, the proximity of each of these areas to the DMH presents the possibility that the effects noted in these studies might actually be mediated through neurons in the latter region. For example, Monda and colleagues had reported that the increases in sympathetic nerve activity to IBAT produced by intracerebroventricular administration of PGE1 in anesthetized rats were suppressed by microinjection of muscimol into the PH (123). However, the dose and volume in which it was injected suggest that spread or diffusion to the relevant thermoregulatory neurons in the DMH might account for the effect noted. Even more importantly, the stereotoxic coordinates targeted in these experiments taken from the atlas of Pellegrino (155) correspond, in fact, more closely to the DMH, as the regions were subsequently delineated in a more current reference work (154; see discussion in Ref. 184). Other reports of a modest reduction in experimentally induced fever after chemical lesioning in either the VMH (124) or the PVN (25) used the excitotoxin ibotenate, an agent thought to act through stimulation of ionotropic glutamate receptors. Given the apparent sensitivity of sympathoexcitatory neurons in the DMH to other ionotropic glutamate receptor agonists (see Search for a hypothalamic thermogenic center and Refs. 45 and 184) and the fact that none of these studies included controls to establish anatomic specificity for their interventions, the possibility of excitotoxonic damage to the DMH seems plausible here as well.

It should be noted that in nearly all of these studies and certainly in those that point directly to the participation of the DMH in fever, the experimental model used involves the central administration of PGE2 in anesthetized preparations. However, anesthesia disrupts normal thermoregulation, so that artificial means are generally used to support basal body temperature in such experiments. Given this, it seems clear that caution must be exercised when extrapolating the results from studies in anesthetized preparations to physiological thermoregulatory processes. Furthermore, as discussed above, the model itself is based upon current long-standing and perhaps overly simplistic hypotheses regarding the central mechanisms and origins of the febrile response. Another model for fever and one that is arguably more “physiological”, involves the systemic administration of LPS in an unanesthetized preparation. As with central administration of PGE2, LPS elicits increases in body temperature, but the response is highly complex and may involve various modes of signaling the CNS (for reviews, see refs. 41, 167, 168). Numerous studies in rats have reported that systemic administration of LPS increases fos expression in the DMH (56, 66, 103, 104, 158, 165, 224), indicating that neurons in the region are activated in this model, and preliminary results suggest that this activation involves neurons in the region that project to the rRP (174). To date, however, no study that has systematically examined the effect of interventions in the DMH on the response to systemic LPS in rats has appeared.

Involved of DMH in Physiological and Pathophysiological Thermoregulatory Phenomena: Avenues for Future Exploration

The finding that neurons in the DMH may signal the activation of premotor sympathetic neurons in the rRP that are aimed at elevating body temperature in cold defense and in fever invites speculation regarding their potential roles in thermoregulatory responses in a variety of additional settings. Among these settings are those associated with chemical signals related to food intake and ingestive behavior, a hypothalamic function that has long been linked with thermoregulation (see Ref. 70). For example, leptin, a peptide best known for its effect on feeding behavior, also produces an increase in body temperature in rats and mice (26, 156, 187, 188) and may play a role in the circadian rhythmicity of body temperature in humans (181). Leptin receptors are found in the DMH (109, 120) and systemic administration of leptin results in fos expression in the region (54), including the dorsal portion where neurons projecting to the rRP are concentrated. Microinjection of leptin into the DMH—but not into the PVN or the VMH—elevates heart rate in anesthetized rats (117), suggesting that the peptide is capable of exciting cardiac sympathoexcitatory rRP-projecting neurons in the region. Most importantly, Morrison has demonstrated that intravenous administration of leptin elicits increases in sympathetic nerve activity to IBAT, IBAT temperature, and heart rate in anesthetized rats, and that these increases are suppressed by stimulation of serotonergic 5-HT1A receptors in the rRP (131). Thus the leptin-induced activation of the rRP and resultant sympathetic thermogenic response may well be a consequence of activation of excitatory projections originating in the DMH. If so, then Morrison’s finding also indicates that manipulation of serotonergic receptors in the rRP may be an effective means of blocking sympathoexcitatory transmission from the DMH (see Chemical signaling in thermoregulatory pathways involving the DMH).

The role of the DMH in drug-induced thermoregulatory disturbances represents another relatively unexplored area ripe for investigation. An example here is presented by the narcotic analgesics. Morphine itself, as well as other drugs and peptides acting at μ-opioid receptors, elicits increases in body temperature in rats (6, 38, 67, 177), perhaps by an action in the POA (163, 205, 207, 214), although a site of action in the periaqueductal grey has also been proposed (178, 211). The hyperthermia produced by systemic administration of morphine is accompanied by increased fos expression in the DMH (182), suggesting that activation of thermogenic mechanisms in the region could be involved. Once again, studies by Morrison’s laboratory that focused principally on the regulation of sympathetic nerve activity to BAT have provided key findings in
support of this idea. Cao and Morrison (32) examined the response evoked by the μ-opioid receptor agonist fentanyl in anesthetized rats. Given either intravenously or intracerebroventricularly, fentanyl evoked increases in renal and IBAT sympathetic nerve activity, IBAT temperature, heart rate, and arterial pressure. The intracerebroventricular fentanyl-induced increases in IBAT sympathetic nerve activity, IBAT temperature, and heart rate were virtually abolished by prior microinjection of muscimol into the DMH, while fentanyl-evoked increases in arterial pressure and renal sympathetic nerve activity were unaffected. Thus neuronal activity in the DMH seems likely to play a role in the hyperthermia seen after systemic administration of narcotic analgesics that act through μ-opioid receptors in rats.

Returning full circle, the role of the DMH-to-rRP circuit in the hyperthermia typically seen in experimental stress represents another promising research avenue. As discussed above, evidence has accrued over the past decade supporting a role for neuronal activity in the DMH in a wide range of physiological responses associated with experimental stress in rats. Stress hyperthermia is an often ignored but well-documented phenomenon known to occur in rats and other mammals (22, 100, 113, 114, 208), including humans (59, 69, 162), and has been proposed to play a role in physiological thermoregulation in some mammals in the wild (134). In the laboratory, the ability of even the mild stress associated with experimental manipulation to elevate body temperature often necessitates careful consideration in the design of studies of the febrile response in conscious animals (e.g. Refs. 166 and 189). Similarities (22, 113, 114, 208) and differences (89) between stress hyperthermia and more conventional fevers have been posited, but the central mechanisms and neural pathways that mediate the former remain less well studied than those responsible for the latter (for a review see Ref. 145). Because sympathetically mediated activation of BAT seems to be involved in stress-induced hyperthermia in the rat (179), a role for activation of excitatory projections from the DMH to the rRP seems highly likely, and our preliminary results support this idea. We have found that in conscious rats, microinjection of saline into the DMH or the PVN in control experiments typically results in an increase in body temperature, likely resulting from the mild stress of experimental manipulation. Similar increases in temperature were also apparent after microinjection of muscimol into the PVN but were entirely absent after otherwise identical microinjection of muscimol into the DMH (Hunt JL, Zaretsky DV, Sarkar S, DiMicco JA, unpublished observations). These findings suggest that inhibition of activity in the DMH can suppress stress-induced hyperthermia and so support a role for neurons in the region in this phenomenon.

Chemical Signaling in Thermoregulatory Pathways Involving DMH: Another Unexplored Frontier

The forgoing provides ample evidence, suggesting an important role for neurons in the DMH—and specifically for those in the region that project to the medullary rRP—in the control of sympathetic thermoregulatory mechanisms in a variety of settings. Now, important questions can be addressed with regard to the neuropharmacology of this anatomically defined pathway. Clearly, activity of relevant thermoregulatory neurons at both the hypothalamic and the brain stem level is regulated by synaptic inhibition and excitation mediated by GABA_A receptors and ionotropic glutamate receptors, respectively (31, 33, 116, 132). However, little else is known about the potential for modulation of transmission in this key pathway by receptors for other neurotransmitters.

One direction that appears promising for future study is the potential involvement of serotonin and serotonergic receptors in the circuit. Serotonin-containing neurons are found in the rRP, and these are known to project to sympathetic regions of the spinal cord. Recent evidence links serotonergic neurons in the rRP to thermoregulation (141). For many years, it has been appreciated that serotonergic drugs have significant effects on body temperature (for a review, see Ref. 40). This is particularly true for agents that act to stimulate 5HT1A receptors, which are well known to evoke pronounced hyperthermia (78, 122), perhaps by acting in the rRP (14, 199). Horie and coworkers (82) found that the increases in heart rate, arterial pressure, and renal sympathetic nerve activity evoked by disinhibition of the DMH in anesthetized rats could be virtually abolished by systemically or intracerebrally administered 8-OH-DPAT, a prototypical 5HT1A receptor agonist. Blessing first reported that systemic administration of this agent could prevent the increases in body temperature and decreased blood flow to the pinna evoked by systemic administration of LPS in rabbits, and that this effect was reversed by the 5HT1A receptor antagonist WAY 100635 (18). Subsequently, microinjection of 8-OH-DPAT into the rRP in conscious rabbits was reported to suppress the sympathetically mediated tachycardia evoked by stress or by LPS (140). As discussed above, activation of BAT evoked by systemic leptin in anesthetized rats can be suppressed by stimulation of 5HT1A receptors in the rRP (131). Together, these findings suggest that sympathoexcitatory transmission from the DMH to the rRP—including that which is relevant to thermoregulation—can be inhibited by stimulation of 5HT1A receptors in the latter region. Given that stress-induced hyperthermia is likely to be signaled through the circuit from the DMH to the rRP, a report that 8-OH-DPAT suppresses this phenomenon in mice (107) provides additional support for both hypotheses.

Perspectives

Thus the DMH has suddenly come to light as a hypothalamic region interposed between classic thermoregulatory neurons in the POA and downstream neurons that ultimately control a variety of mechanisms relevant to body temperature in rats. Evidence for this idea is strongest with regard to projections to sympathetic premotor neurons in the rRP—and perhaps the cPAG—that regulate BAT. Further insights into signaling related to thermoregulation through projections from the DMH to these downstream regions will undoubtedly emerge from characterization of the phenotype of the specific neurons that contribute to these pathways. However, the literature also hints at the participation of neurons in the DMH in thermoregulatory endocrine adjustments, somatomotor activity, and even behavior (see Ref. 118). If these possibilities are borne out by the results of future studies, then the DMH may assume the role of a key hypothalamic site responsible for integrating the control and coordination of multiple effector systems that mediate thermoregulation in mammals. How this new function for the region might relate to its better established role in physiolog-
ical and behavioral responses to exteroceptive stress (for reviews, see Refs. 50 and 51) is an issue that invites numerous questions. For example, responses to stress resemble in many ways the physiological changes seen in exposure to cold (i.e., “cold stress”) or accompanying the innate immune response, but the resemblance is not perfect. Do these different circumstances recruit a slightly different subset of neurons in the DMH, or is the response shaped and modified by the involvement of other brain regions? Similarly, although the neurons controlling sympathetic nervous responses to BAT and the heart have been localized to a distinct subregion of the DMH, those responsible for the accompanying neuroendocrine and behavioral effects have not. As the afferent and efferent neural circuitry relevant to these components becomes clear, the stage will be set for studies that will likewise clarify the functional neuroanatomy of the DMH.

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