A New Version of the Thalamic Disinhibition Hypothesis of Central Pain

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The hypothesis is presented that central pain is due to the disruption of thermosensory integration and the loss of cold inhibition of burning pain. This is a new variation on the thalamic disinhibition hypothesis originally proposed by H. Head and G. Holmes in 1911 (Brain 34:102–254). The thermal grill illusion of pain provides a model for this concept. Functional anatomic substrates are described that provide a sound framework for the hypothesis. Predictions are made and unresolved issues are addressed that provide opportunities to test this hypothesis. **Key words:** *pain, thermoreception, thalamus, cingulate, insula.*

The intractable pain that can appear following a stroke or other lesion of the central nervous system is a central pain syndrome; it occurs entirely within the brain. Central pain has always been intriguing, because it is clear that to understand this syndrome means understanding something critical about how pain is represented in the brain. We are approaching this goal, albeit incrementally. This essay presents an informal description of a new hypothesis for a possible cause of central pain, which has been alluded to in earlier publications [34,43]. This hypothesis builds directly on the oldest proposal for the basis of central pain, the thalamic disinhibition hypothesis of Head and Holmes [66]. It is presented with the understanding that there may be other causes of central pain. I hope this description will be understandable to all professionals who work in the field of pain and that the dialogue encouraged by this forum will lead to further insights into the representation of pain in the brain.

This contribution should be viewed as an addendum to the recent book on central pain edited by Casey [26]. The many outstanding contributions in this volume summarize well the history, findings, ideas, and references relevant to central pain. Other reviews of note have been published by Pagni [96], Boivie and Leijon [12], Bowsher [15], and Schott [107].

THE HYPOTHESIS

Briefly stated, the hypothesis is that central pain patients experience a phantom burning feeling that resembles the burn of cold pain, because the inhibition of pain normally induced by thermosensory integration has been disrupted. In central pain, the disruption of thermal sensibility results in the loss of the cold-induced inhibition of pain and the disinhibition of cold-evoked burning pain.

The hypothesis is based on the concept that central pain is a release phenomenon resulting from the disruption of normal integrative controls on pain processing. I propose that the integration that is disrupted is part of a general homeostatic (or thermoregulatory) interaction between thermosensory activity and polymodal nociceptive activity. This integration occurs in a network that motivates homeostatically appropriate behavior in response to a dangerous condition in the body. One particular interaction disrupted is the cold-induced inhibition of pain. Inhibition of cold-evoked polymodal nociceptive activity by thermoreceptive-specific cold activity manifests the neural differentiation of noxious cold from innocuous cool, generating a contrasting sensation of burning pain and contrasting motivational activity. Disruption of this integration by a lesion of the main thermosen-

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sory pathway in central pain patients effectively disinhibits this burning sensation, releasing development of an ongoing pain that can be exacerbated by cold at temperatures that are normally perceived as innocuous cool.

The hypothesis is placed in a functional anatomic framework. The disruption of thermosensory activity results from damage to the lateral lamina I spinothalamocortical pathway to parietoinsular cortex. This disinhibits polymodal nociceptive activity in the medial lamina I spinothalamocortical pathway to the anterior cingulate cortex. This medial pathway is part of a homeostatic network (the limbic or emotional motor system) that motivates behavior appropriate for survival. The site (or sites) of the inhibitory interaction remains to be determined.

The hypothesis is based on the characteristics of central pain and on several results from basic research. Because some readers may not be familiar with central pain syndromes, I begin the explanation there.

CHARACTERISTICS OF CENTRAL PAIN

Normally, pain is sensed when an abnormal condition in the body activates primary afferent nociceptors, and the pain signals that there is something dangerously wrong with the tissues of the body. In the central pain syndromes, pain is caused by a lesion of the central nervous system. The substance of the spinal cord and brain is insensate. In contrast, the meninges surrounding them are innervated by sensory afferents that probably are the basis for many headaches and backaches. Thus, this can only mean that in central pain the lesion has either enabled or released activity in parts of the brain where such activity engenders a subjective pain sensation.

The main characteristics of the central pain syndromes are well summarized by Casey [26], Boivie and Leijon [12], and Bowsher [15]. A variety of other symptoms (such as paresis and dystonia) may present, and lesions at various locations may cause central pain with overlapping characteristics, perhaps by different mechanisms, but the majority of central pain patients have these core symptoms. An ongoing pain is experienced that is described as burning, aching, icelike, and tingling, and that is generally localized to deep tissues or to skin and deep tissues. The pain is located on one side of the body, frequently the hemibody or the face or upper or lower limb. It can often be exacerbated by normally innocuous stimuli (allodynia), particularly by cool stimuli, sometimes by light touch, and rarely by warmth. An emotional overreaction is not uncommon (hyperpathia), and the pain is often increased by stress or anxiety.

Sensory testing of the peripheral region where the pain is experienced generally shows that it is located within a region of paradoxical hypoalgesia, or lowered sensitivity to painful stimuli (pinprick, often noxious heat). Significantly, within the hypoesthetic zone, the painful region is most closely correlated with a zone of decreased sensitivity to thermal stimuli (particularly cold, but also warm). The pain may even be proportional to the loss of thermal sensibility [15]. In some cases, such thermanesthesia is the only demonstrable sensory abnormality. This cardinal observation, recently emphasized by Boivie and Leijon [12] and by Bowsher [15], is critical to the present proposal.

Interestingly, there are often signs of autonomic impairment, and the area in which the pain is greatest is cooler and vasoconstricted [15]. In addition, there may or may not be a delay in the onset of ongoing pain following stroke or trauma from days to years. Central pain patients sometimes obtain relief from amitriptyline, a tricyclic antidepressant with actions on multiple neurotransmitter systems, but rarely from analgesics, including opiates. Intravenous propofol (Diprivan, a gamma-aminobutyric acidergic antagonist) can immediately, though temporarily, alleviate the allodynia and ongoing pain at subanesthetic doses [16]. Central pain is estimated to occur in 2 to 8% of all stroke cases, at least 20% of strokes involving the posterolateral thalamus, and about 25 to 40% of spinal cord injury and multiple sclerosis cases [2,26]. The suicide rate is said to be high.

The characteristic lesion underlying central pain was first thought to be located in the posterolateral thalamus (an infarct of the thalamogeniculate artery), as described by Dejerine and Roussy, who coined the term *thalamic syndrome* [49]. Now it is recognized that lesions at the spinal, medullary, brainstem, thalamic, capsular, and cortical levels can produce a similar set of core symptoms. Although some have suggested that involvement of the lemniscal pathway was important, most clinical reviewers agree that the critical feature is involvement of the lateral spinothalamocortical pathway, resulting in loss of pain and temperature sensitivity [12,15,26,96,107]. Thus, the release of ongoing burning pain in the portion of the body rendered partially insensitive suggests that central pain is an unmasking or disinhibitory phenomenon, as Head and Holmes first proposed in 1911 based on Hughlings Jackson's tenet that a lesion cannot itself cause a positive effect.

THE ORIGINAL HYPOTHESIS OF HEAD AND HOLMES

The classic study of (thalamic) central pain patients by Head and Holmes provided many observations that have been repeatedly confirmed [66]. Based on their extraordinarily careful work, they made what I feel was a prescient set of proposals for the cause of the central pain syndrome. Their ideas are summarized in Figure 1,

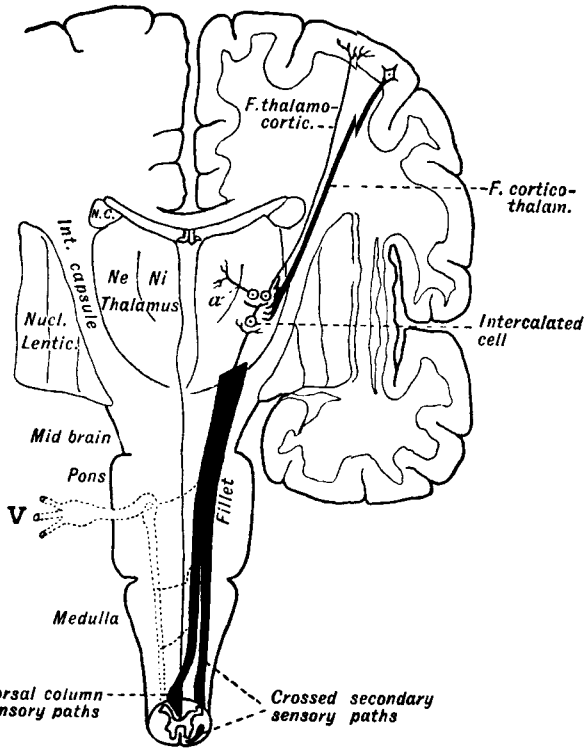

Fig. 1. Drawing Head and Holmes used to present their original hypothesis for the basis of (thalamic) central pain. COLD, cooling-specific lamina I cells; HPC, polymodal nociceptive lamina I cells; STT, spinothalamic tract; VMpo, posterior portion of ventral medial nucleus; MDvc, ventral caudal portion of medial dorsal nucleus; PAG, periaqueductal gray; PB, parabrachial nucleus. (From Head and Holmes [66], with permission.)

which is reproduced from their article. Their hypothesis has formed the basis for all succeeding notions of the central representation of pain, in particular the enduring notion that the lateral thalamus is involved in the discriminative aspects of pain and medial thalamus in the emotional aspects of pain sensation [93].

First, they deduced that the demonstrable sensory loss in these patients meant that the posterolateral thalamus must contain a specific substrate for the discriminative sensations of pain and temperature, which was damaged by the lesion. Recent work in my laboratory and others' laboratories has provided direct evidence for such a substrate in monkey and human (VMpo, described below). It is penetrated by several moderately large transverse vessels, which might indeed render it susceptible to cardiovascular insult.

Second, they inferred that the loss of this lateral thalamic substrate for pain resulted in the disinhibition or release of the medial thalamus, which was thought to be important for the emotional aspects of pain. They made this conjecture believing that cortical lesions rarely affect pain sensation, so that the hyperpathic pain in central pain patients must be engendered in the thalamus, in particular in the undisturbed medial thalamus. A recent clinical survey has confirmed that lesions of the thalamus produce central pain only if they include the posterolateral thalamus, and that lesions restricted to the medial thalamus never cause central pain [11]. In my opinion, Head and Holmes' suggestion that pain sensation occurs in the medial thalamus (the "essential centre") reflects their basic cartesian focus, despite their vague awareness of the intimate cortical and subcortical interconnectivity of the medial thalamus. The present hypothesis retains the essence of their fundamental insight that activity in the lateral thalamic pathway is responsible for inhibition of a medial thalamic nociceptive pathway.

Third, they proposed that the inhibitory pathway disrupted in central pain patients extends directly from the lateral to the medial thalamus. In this conjecture, they erred because there are few such intrathalamic connections. Recent proposals by Cesaro et al. [29] and by Jeanmonod et al. [75] have revived this intrathalamic notion, with the interesting suggestion of an indirect inhibitory interaction between lateral and medial (intralaminar) thalamus via the thalamic reticular nucleus; however, anatomic evidence to support these proposals in the primate is similarly lacking.

Apparently, Head and Holmes also believed that the inhibition and the excitation of pain-related activity in the medial thalamus both derived from the pain-related activity in the posterolateral thalamus, though they did not explain how the inhibition might be lost but the excitation persist. Later, authors addressed this discrepancy by hypothesizing an excitatory multisynaptic spinoreticulothalamic pathway ascending to medial thalamus via the brainstem, converging there with the so-called paleospinothalamic projection to the intralaminar nuclei [9,15,92]. Today, there is clear evidence of direct spinothalamic input to a discrete medial thalamic site involved in pain sensation (MDvc, described below), yet the involvement of alternate pathways must still be considered.

The present hypothesis builds directly on the insights of Head and Holmes and incorporates new knowledge regarding pain and temperature processing and the functional anatomy of the spinothalamocortical pathways. As in their proposal, this model includes a specific spinothalamocortical pathway for pain and temperature sensation relayed in posterolateral thalamus, and the disruption of this pathway is responsible for disinhibition of the medial pathway. The present hypothesis differs from Head and Holmes' in two significant ways, discussed in order below. First, this model proposes that it is the thermoreceptive component, rather than the pain component, of the lateral spinothalamocortical pathway

that is the critical source of inhibition in the medial pathway. Second, this model incorporates a specific substrate in the medial thalamus that relays direct spinothalamocortical polymodal nociceptive activity to a limbic (affective) network involved in motivating homeostatically appropriate behavior.

THE COLD-INDUCED INHIBITION OF PAIN

Pain and temperature sensations signal the condition of the tissues of the body. Both nociceptive and thermoreceptive afferent activity drive homeostatic mechanisms at spinal, brainstem, and forebrain levels, and both generate obligatory, characteristic affective/motivational states (see Craig [37]). The pathways for specific pain and temperature activity in the central nervous system are anatomically and functionally overlapping. These properties are certainly commensurate with the possibility of fundamental interactions between these modalities. Integration of thermosensory and pain-related activity in a mammalian organism is necessary for homeostasis and survival.

It is well known that thermal stimuli can be highly therapeutic for clinical pain, and recently it has been appreciated that their effects include central as well as peripheral interactions. Evidence that a central interaction occurs is provided by the observation that cold stimuli can reduce the pain reported on electrical stimulation of a peripheral nerve [8]. There is also experimental evidence of an interaction between warmth and pain [28].

The effect of a selective pressure block of peripheral nerve A-fiber conduction in humans is particularly revealing [59,119,122]. When conduction is blocked and cold sensitivity is eliminated, cold (and also pinch) evokes a painful, burning sensation at temperatures that rise from the normal 15°C threshold of noxious cold to as high as 24°C. This indicates that cold-evoked activity in C-fiber polymodal nociceptors produces a perception of burning pain. Direct physiologic evidence confirms that cold can activate some polymodal C nociceptors at such innocuous temperatures [23,62,80]. Similarly, cold water injected into a vein causes a graded sensation of burning pain, presumably by activating deep polymodal C nociceptors surrounding the vessel without activating cutaneous A-delta cold-specific fibers [60]. These findings suggest that C-fiber-elicited burning pain is normally masked centrally by activity in the specific A-delta thermoreceptors that produce the sensation of cold.

A striking demonstration of the disinhibition of pain by anomalous thermosensory integration is provided by the thermal grill illusion, first demonstrated by Thunberg in Sweden in 1896 [115]. The illusion is generated by presentation of innocuous cool (20°C) and warm (40°C) stimuli together in a spatially unusual, interlaced fashion. (It can be experienced at the Ontario Science Center in Toronto or at the Epcot Center at Disney World. I learned of it when U. Norrsell responded to my queries about possible interactions between temperature and pain by referring me to Boring's (1942) experimental psychology textbook [13].) The salient feature of the illusion is that the addition of interlaced warm bars to a cool stimulus results in a diminished sensation of cold (consistent with spatial summation), but, in addition, a sensation of burning, icelike pain. The sensation resembles the burn of cold pain and the burning pain evoked by cold following peripheral nerve A-fiber conduction block. Using modern psychophysical methods, my colleague M. Catherine Bushnell and I confirmed that this is a robust illusion [39].

The thermal grill illusion of pain can be explained physiologically as an unmasking phenomenon based on the activity of lamina I spinothalamic neurons [34,39], which form the pain and temperature pathways to be described below. The cool bars in the grill activate just two types of neurons: innocuous cooling-specific (COLD) lamina I cells, and polymodal nociceptive (HPC) lamina I cells that respond to noxious heat, pinch, and cold. (Nociceptive-specific [NS] lamina I spinothalamic cells and wide-dynamic-range [WDR] lamina I and lamina V nociceptive cells are not excited by the grill.) The COLD cells have a threshold near normal skin temperature (ca. 34°C), and they are normally more active at innocuous cold temperatures than the HPC cells, the threshold of which is near comfortable room temperature (ca. 24°C). At noxious cold temperatures (below 15°C), HPC cell activity predominates. With a thermal grill stimulus, the interlaced warm bars reduce the activity of COLD cells by half, but the cold-evoked activity of HPC spinothalamic neurons is unaffected. Thus, the grill effectively induces a shift in the relative balance of activity in favor of HPC cells, like that induced by noxious cold.

These findings have several implications. First, they indicate that COLD lamina I spinothalamic neurons, which convey specific A-delta thermoreceptive activity, provide the thermosensory pathway for cold sensation. Similarly, they indicate that HPC lamina I spinothalamic neurons, which convey polymodal C-fiber nociceptive activity, provide the basis for a sensation of burning pain. These conclusions are corroborated by the opposing effects that morphine has on these cell types; morphine inhibits HPC cells, whereas it enhances the activity of COLD cells [37]. Psychophysical differences between innocuous and noxious cold sensations are also consistent with these conclusions [30,31]. (Warmth, which inhibits COLD cells, may also have opposite effects on HPC cells.)

Second, COLD cell activity must interact with HPC

activity at thalamocortical levels (Fig. 2) for the unmasking to occur. The simplest model of this interaction is formed by subtracting mean COLD discharge from mean HPC discharge. This is a valid model, because it successfully predicts that the mean pain rating produced by the grill is quantitatively equivalent to that produced by a uniform noxious cold stimulus of 10°C. Thus, the thermal grill illusion can be explained by a reduction in supraspinal inhibition of the polymodal nociceptive HPC pathway by the thermoreceptive COLD pathway, that is, by a reduction in the cold-induced inhibition of pain.

Third, these findings demonstrate that the thermal grill evokes a pattern of neural activity that corresponds to the pattern evoked by noxious cold, albeit with normally innocuous thermal stimuli. This supports the inference that the burning pain elicited by the thermal grill is the same sensation as the burn of cold pain. Bushnell and I recently confirmed this congruence at the level of the cortex with positron emission tomography (PET) functional imaging in humans [42]. The PET data show that the same four areas of cortex are activated by noxious cold and by the thermal grill, with no statistical differences.

These PET data also reveal the cortical location of activity unmasked by the grill. Whereas separate cool and warm stimuli applied to the glabrous hand activate insular and somatosensory cortical areas, the combination of these stimuli in the thermal grill activates these areas plus an additional area in the fundus of the anterior cingulate sulcus. This cortical area is also activated by noxious cold and heat, as observed in prior studies [27,76,114]; therefore, anterior cingulate activation appears to be selectively associated with the perception of thermal pain, whether real or illusory. This conclusion is strongly supported by statistical comparisons of the areas activated by cool and noxious cold or by warm and noxious heat, applied to the hand with the same thermode, which in each case show a significant difference only in this anterior cingulate region. The activation in anterior cingulate cortex unmasked by the thermal grill illusion indicates that this site plays a critical role in the burning pain sensation caused by disinhibited lamina I HPC activity.

Thus, the thermal grill illusion demonstrates that normal thermosensory integration inhibits pain sensation. In the grill, a selective reduction of specific thermoreceptive (cold) activity diminishes the cold-induced inhibition of pain and unmasks the underlying cold-evoked activity in the polymodal nociceptive pathway that causes burning pain. The present hypothesis proposes that disruption of thermosensory integration, in particular the cold-induced inhibition of pain, also underlies the central pain syndrome. The functional anatomic observations described below provide a sound framework for these findings.

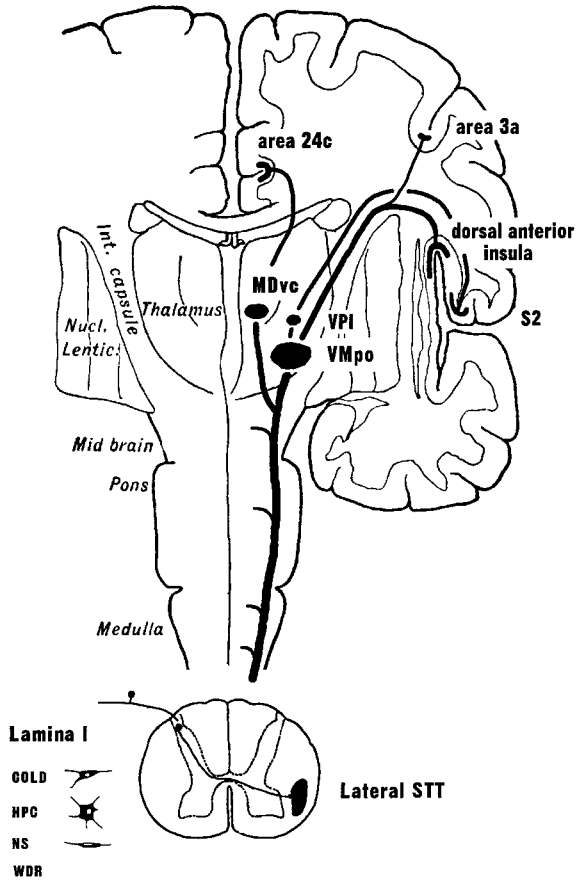

Fig. 2. Drawing representing the concept that cooling-specific (COLD) lamina I activity inhibits polymodal nociceptive (HPC) activity at thalamocortical levels, based on results obtained with the thermal grill. NS, nociceptive-specific tracts; WDR, wide-dynamic-range cells; STT, spinothalamic neurons; VPI, ventral posterior inferior nucleus; VMpo, posterior portion of ventral medial nucleus; MDvc, ventral caudal portion of medial dorsal nucleus.

THE LATERAL SPINOTHALAMOCORTICAL PATHWAY

The clinical observation that central pain is caused by a lesion of the lateral spinothalamocortical pathway that is critical for pain and temperature sensation strongly suggests consideration of the role of the ascending pathway, which originates in lamina I of the dorsal horn, based on its functional anatomic characteristics. The lamina I spinothalamic projection comprises unique sets of specific nociceptive and thermoreceptive neurons. Their activity is sufficient for both temperature and pain sensations, as shown by the findings with the thermal grill illusion. Contralaterally ascending lamina I axons are concentrated in the middle of the lateral funiculus, that is, in the classic lateral spinothalamic tract, the

critical spinal location for ascending pain and temperature activity [37]. As summarized in Figure 3, the termination sites of lamina I spinothalamic axons in the lateral and the medial thalamus of primates project in turn to four cortical regions; these correspond one-to-one with the cortical sites activated in PET- functional imaging studies of pain and temperature in humans. Furthermore, the lateral parietoinsular cortical projections of this pathway match the locations of capsular and cortical lesions that produce the hypoalgesia and thermanesthesia associated with central pain syndrome [7,12,85,106].

The primary lamina I spinothalamic termination site is a dedicated relay nucleus in the posterolateral thalamus called VMpo (posterior part of the ventral medial nucleus), which receives dense, topographically organized input almost exclusively from lamina I neurons [40]. In monkeys, VMpo contains specific nociceptive and thermoreceptive (cold) neurons that have small contralateral receptive fields and that are topographically organized consistent with the anatomic organization. In humans, stimulation in the region of the posterolateral thalamus in which VMpo can be identified histologically [40] evokes discretely localized pain or cold sensations [52,88], and a few nociceptive and thermoreceptive (cold) cells have been recorded at these sites [47,87]. A lesion in this region in humans disrupts pain and temperature sensation and can cause central pain [12,48,49]. These findings indicate that VMpo is a specific substrate for pain and temperature sensation in the posterolateral thalamus.

The cortical projections of the primate VMpo corroborate this conclusion. Findings in monkeys indicate that VMpo projects topographically to the dorsal part of the mid/anterior insular cortex, with a collateral projection to area 3a in the fundus of the central sulcus [36]. This region of insular cortex contains specific nociceptive and thermoreceptive neurons [51]. Similarly, functional imaging studies show strong activation of mid/anterior insular cortex in humans by both noxious and innocuous thermal stimuli, as well as activation in the region of the central sulcus that may be focused in area 3a in humans and monkeys [27,42,116].

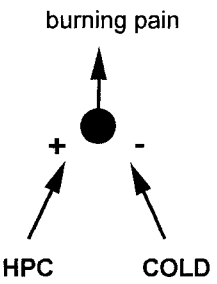

Fig. 3. Schematic representation of the lamina I spinothalamocortical projections, based on work in this laboratory. HPC, polymodal nociceptive lamina I cells. Cold, thermoreceptive-(cooling) specific lamina I cells.

Additional lateral spinothalamic lamina I terminations occur in the ventral posterior inferior nucleus (VPI), which neighbors VMpo. Both NS and WDR neurons have been recorded in VPI [4]. It projects in turn to the second somatosensory region (S2) in the lateral operculum near the insula [58], which may contain several distinct cortical areas [82]. This region is also activated in humans by noxious stimuli [17,27,76,112,114]. The PET imaging data indicate that cold stimuli activate the region of S2 in addition to the insular cortex [42], but to date thermoreceptive-specific neurons have been recorded in VMpo and the insula and not in VPI or the S2 region. Cold-induced PET activity in S2 could result from the phasic activation of slowly adapting mechanoreceptors [20,22].

Thus, the components of this lateral spinothalamocortical lamina I pathway fit with the locations of infra- and supratentorial lesions that produce the hypalgesia and thermanesthesia associated with central pain in humans. The nucleus VMpo fulfills the prediction made by Head and Holmes of a posterolateral thalamic relay nucleus for discriminative pain and temperature sensation. The buried insular location of the cortical projection field of VMpo partially exonerates the erroneous inference by Head and Holmes that the cortex is not involved in pain and temperature sensation. The present hypothesis posits that a lesion of this pathway disrupts thermal sensibility and the cold-induced inhibition of pain, thereby releasing the burning, icelike sensation of central pain.

Any general hypothesis regarding pain must also incorporate other projections to lateral thalamus that ascend in the ventral (or anterior) spinothalamic tract, which early clinical lesion studies concluded was associated with crude somatosensation and proprioception [57,84,90]. These projections originate from large spinal cells in the deep dorsal horn (lamina V) and in the intermediate spinal gray (lamina VII). Lamina V cells are primarily modality-ambiguous WDR somatosensory cells, and lamina VII cells are complex proprioceptive and somatosensory cells, though NS cells can be found in these sites as well [56,101,120]. WDR spinothalamic neurons have received considerable experimental attention with respect to pain. Their activity can be sensitized by stimuli that produce hyperalgesia [111], and their responses to noxious thermal stimuli are correlated with behavioral response movements [89]. Stimulation of the anterolateral quadrant using parameters appropriate for activating lamina V–VII spinothalamic axons can elicit pain in chronic pain patients [91]. Many lamina V–VII

spinothalamic cells project to motor-related thalamic nuclei (the ventral lateral and intralaminar nuclei [3,6,41]), but others terminate in bursts ("archipelago") within the lemniscal ventroposterior nucleus (VP) around neurons that may project to the superficial rather than the middle layers of somatosensory S1 cortex [103,108]. Accordingly, WDR and NS cells have been recorded in VP and in S1 cortex [22,25,77,78]. Lidocaine injection in monkey VP diminishes behavioral detection of noxious or cold stimuli [53], though the effect appears to be most acute if the injection involves posterior thalamus (that is, VMpo). Stimulation in VP can sometimes produce pain in certain chronic pain patients [46], and a relationship of ongoing pain to gamma-aminobutyric acid-induced bursting activity caused by low-threshold calcium channels in deafferented VP neurons has been suggested [86].

Thus, these ventral spinothalamic tract cells must also be involved in pain processing; however, their significance for central pain is unclear. Stimulation in VP and S1 cortex in humans rarely causes pain in nonpain patients, and actually alleviates chronic pain for many patients [63]. Similarly, lesions of S1 cortex rarely produce hypalgesia or affect central pain [99]. One suggestion is that the role of lamina V–VII WDR cells may be modulation of background inhibition, or gain control, in S1 [100]. Accordingly, recent imaging data indicate that noxious heat inhibits S1 activity in area 3b but activates area 3a [5,116]. Perhaps most significantly for the present hypothesis, lamina V–VII WDR cells are not involved in innocuous thermoreception, loss of which may be the critical factor in most cases of central pain. Nonetheless, the possibility must be considered that spared activity in lamina V–VII cells that project to the thalamus or the brainstem may contribute to the mechanical allodynia observed in some central pain patients and, perhaps, the ongoing pain.

THE MEDIAL SPINOTHALAMOCORTICAL PATHWAY

Following the first demonstration of direct spinothalamic input to the intralaminar nuclei in medial thalamus by Clark [32], investigators considered that these projections might provide the basis for the involvement of medial thalamus in pain proposed by Head and Holmes [66]. As a result, ablation of the CM-Pf (centré median–parafascicular) complex for pain was attempted by neurosurgeons in the 1960s [63], with inconsistent results. Modern findings indicate that Pf and CL (central lateral nucleus) receive moderate spinothalamic input, while CM does not receive any [3,19]. Our present knowledge of the connectivity of the intralaminar nuclei (ie, convergence of cerebellar, pallidal, nigral, collicular, and brainstem inputs and projections to striatum and motor cortex) supports the inference that spinothalamic input to these nuclei, which originates primarily from complex lamina VII cells, is involved in sensorimotor integration.

More recent anatomic work has demonstrated a novel spinothalamic termination site in a compact posteromedial region of primate thalamus referred to as MDvc (ventral caudal part of the medial dorsal nucleus [43,61]). Like VMpo, this is also a topographic projection that may receive spinothalamic input almost exclusively from lamina I neurons [1]. Other sources of brainstem and forebrain input have not yet been identified, but probably include the amygdala [81]. The MDvc projects in turn to area 24c in the fundus of the anterior cingulate sulcus [43]. As noted above, functional imaging studies indicate that this portion of limbic cortex is activated by noxious thermal stimuli in humans [76,114], and that it is a critical site for thermal pain [42]. Recordings of nociceptive neurons in anterior cingulate cortex have been reported in humans [72], and there are similar reports in rabbits and rats that are functionally supportive [109,121] but may not be comparable anatomically. There have been reports that stimulation in posteromedial thalamus in humans can evoke pain [74,105], that medial thalamic lesions have alleviated chronic pain in some cases [74,104], and that medial thalamus in humans contains nociceptive neurons [105], but it is difficult to know whether or not these sites included MDvc. Based on cytoarchitectonic criteria, MDvc can readily be observed in coronal sections through the posteromedial aspect of human thalamus, a region labeled in some atlases as CL [67].

These findings suggest that MDvc could be the source of pain-related activation of anterior cingulate cortex, and therefore a medial thalamic substrate with a key role in the affective/motivational aspects of pain. Earlier physiologic recordings in awake monkeys found nociceptive-specific neurons in medial thalamus, reportedly in CM, Pf, and CL, whose activity depended on behavioral state [21,25], and it is possible that some of these were in MDvc. Evidence newly obtained in this laboratory in barbiturate-anesthetized monkeys indicates that MDvc contains a concentration of nociceptive-specific neurons with large, sometimes bilateral, receptive fields [38]. Most notably, the ongoing activity of many MDvc neurons can be inhibited by innocuous thermal (cool, warm) stimuli, and some can be inhibited by pinch applied outside the excitatory receptive field (see also Bushnell and Duncan [21]). This finding is strongly reminiscent of the "essential centre," which Head and Holmes predicted would be disinhibited by disruption of the lateral pain and temperature pathway.

CONCLUSIONS

These observations suggest a functional anatomic model (Fig. 4) that embodies the present hypothesis for the basis of central pain. The model is of course incomplete, yet it forms a predictive framework that can be adequately tested. In general terms, the new hypothesis states that a lesion that interferes with the output of the thermosensory (enteroceptive) area in the insula disinhibits a limbic network involving the anterior cingulate that engenders thermoregulatory (homeostatic) motivation. The simplest schema is that disruption of the COLD representation in the insula releases HPC activation of the anterior cingulate, but for reasons to be discussed, this is probably too simple.

For central pain to occur, a lesion of the lateral lamina I spinothalamocortical pathway must occur that is sufficiently large to produce contralateral sensory symptoms. The common feature of all lesions that produce central pain appears to be deafferentation of the pain and temperature representation in the mid/anterior insular cortex. Thermal sensibility must be lost or severely affected. The data described above indicate that this means the lesion disrupts the lamina I COLD pathway via the lateral funiculus to VMpo to the insula. Whether the parietal opercular region of S2 must be included is uncertain.

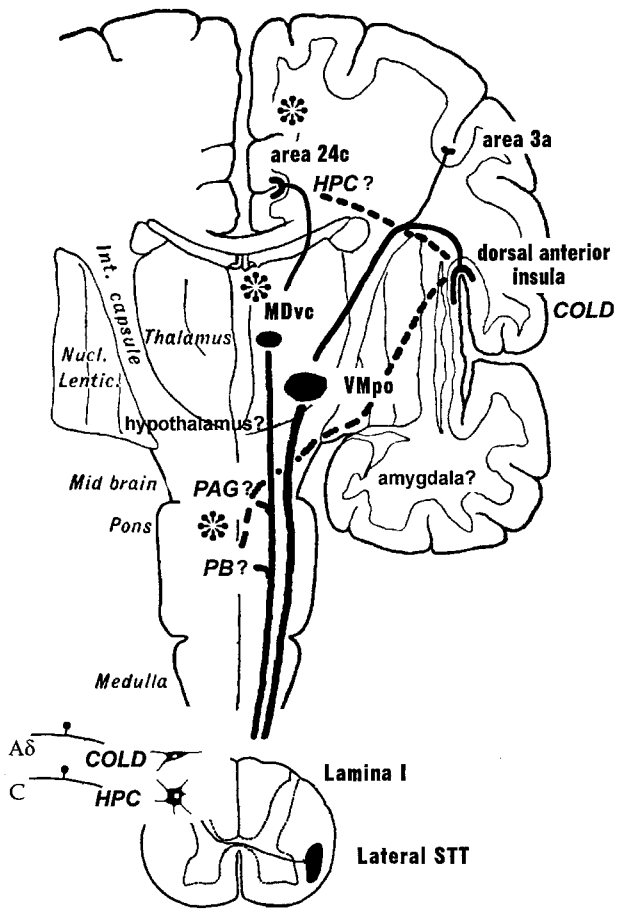

Fig. 4. Schematic representing several possible sites at which efferents from the insular lamina I thermoreceptive zone might inhibit pain-related activity ascending to the anterior cingulate.

Both cold and warm sensibilities are commonly affected in central pain, suggesting that a warm-sensitive thermosensory pathway might also be involved. Thermosensory integration necessarily involves both cold and warm sensibilities in a unified sensory dimension; as the thermal grill shows, cold and warm are not perceived simultaneously. Further, warm-specific projection neurons have rarely been observed. Warm sensation could be represented centrally by the graded inhibition that warmth produces in the activity of the COLD pathway; if so, then this might explain why warm sensation is more susceptible to disruption, as sometimes reported clinically [65]. Warmth produces a different pattern of cortical activation from cold [42], yet the pattern includes the insula, so such differences may reflect the cortical processing of warm-induced inhibition of COLD activity.

Along with temperature sensation, acute pain sensitivity is usually, but not necessarily, also reduced in central pain patients. Because both pain and temperature sensations are subserved by the lateral lamina I spinothalamocortical pathway to the insula, a lesion affecting one would usually affect both.

The correlation of the ongoing pain with the region and degree of thermosensory dysfunction certainly implies that central pain is a release phenomenon. The release is immediate in some cases, but delayed in others, perhaps until the lesion is enlarged by secondary insult or degeneration. There may be changes in transmitter or receptor levels [102], but because immediate onset and reversal can occur, such up- or down-regulation may have a secondary role [16,44,107]. Nonetheless, central pain develops following some, but not all, appropriately placed lesions; therefore, other factors must affect the integration that is disrupted by thermosensory dysfunction (see below).

In this model, then, central pain results from the loss of the COLD sensory pathway to the insular cortex because this disinhibits the integration in a pathway that engenders burning pain. In short, the thermosensory integration responsible for the cold-induced inhibition of pain has been disrupted. Therefore, it is the disruption of the corticocortical and descending output from the thermosensory region in the insular cortex that must be critical to the release of burning pain.

This is similar to the process that can explain the thermal grill illusion, which suggests that the sensation experienced by central pain patients is the same as that evoked by the thermal grill illusion of pain. A study of the

effect of the grill stimulus on the two sides of central pain patients could address this possibility. It should be ineffective (or simply be an allodynic cold stimulus) on the affected side of central pain patients, because the mechanism for cold-induced inhibition of pain would already be disrupted, and the patients may be able to relate the subjective sensation caused by the grill to their ongoing pain. This can be tested psychophysically if patients are willing and able to be temporarily drug-free. A recent study of multiple sclerosis patients (without central pain) suggests that decreased thermal sensitivity is correlated with increased warming-induced release (equivalent to decreased cold-induced inhibition) of cold-evoked heat pain [65], which is consistent with this hypothesis.

The functional imaging observations of the thermal grill illusion show that it unmasks activity in the medial pathway to the anterior cingulate cortex, activity that is critical for the perception of burning pain. This suggests that in central pain it may be this medial pain pathway that has become disinhibited, which is reminiscent of the conjecture by Head and Holmes. These considerations indicate that MDvc in the medial thalamus may be a critical site for the cold-induced inhibition of pain-related activity ascending to the anterior cingulate.

Functional imaging studies of central or chronic pain patients have so far produced inconsistent results with regard to identifying the locus of pain-related activity (reviewed by Schott [107]). Increased activation of thalamus or the anterior cingulate has been described by some [29,70]; however, decreased thalamic and parietal cortical activity has been described by others [50,68,73,97]. It is unclear whether such global inhibition represents a compensatory mechanism [107] or dysfunction of inhibitory regulation [24]. Nonetheless, the problems inherent in obtaining controlled populations of patients for functional imaging limit this approach until experimental single-patient PET scanning studies can be performed.

If it is the disruption of cold inhibition of nociceptive activity in the medial pain pathway that is a critical feature underlying central pain, then identifying the mechanism for such inhibition is important. The simplest possible organization would be direct COLD-activated corticocortical interactions between the insula and the anterior cingulate [117], with inhibition (or disfacilitation) of MDvc as a consequence of (bilateral) corticothalamic activity from the cingulate. Alternatively, inhibition of the medial pathway could involve other insular projections to limbic (ie, homeostatic, thermoregulatory) forebrain regions that project to MD, such as the hypothalamus, amygdala, and periaqueductal gray. In my opinion, descending projections from insular cortex to brainstem homeostatic integration sites are also likely involved. This latter possibility resembles a recent description of descending antinociceptive controls from the rostral agranular insula in the rat [18].

Another alternative to explain cold-induced inhibition of the medial pathway would be the presence of direct ascending thermosensory input to MDvc with a local inhibitory action, such as has been found in the cat's analog of MDvc, the nucleus submedius (Sm). Recent physiologic and ultrastructural evidence indicates that Sm receives convergent input from lamina I COLD and nociceptive cells, but that the COLD fibers appear to terminate on gamma-aminobutyric acidergic inhibitory interneurons (presynaptic dendrites) rather than on the thalamocortical relay neurons, which receive the nociceptive input [55]. The possibility that this uncomplicated anatomic substrate for cold-induced inhibition of nociception might be present also in the primate can be examined first by retrograde identification of the morphologic types of lamina I cells that project to MDvc, because COLD neurons are pyramidal cells [64], as well as by using the ultrastructural techniques used in the cat.

Incidentally, the source of nociceptive activation of the medial pathway is an issue that also needs to be examined further. The simplest schema would be that lamina I HPC neurons project to MDvc, which would explain the results obtained with the thermal grill. Retrograde analysis of the input to MDvc can determine whether HPC lamina I neurons project to MDvc, because they are multipolar cells [64]. In addition, polymodal noxious stimuli (other than the thermal grill) normally activate WDR lamina I and V spinothalamic cells, so their involvement in the integration in MDvc and the cingulate should also be reexamined. Furthermore, homeostatic regions in the brainstem that receive bilateral lamina I projections and have projections to the thalamus may also be involved, such as the medullary dorsal reticular nucleus [118] and the dorsolateral pons or the periaqueductal gray [35].

In my opinion, it seems likely that cold-induced inhibition of polymodal nociceptive activity in the medial pathway may occur by actions at several levels. There is probably a global opponent organization between COLD and HPC activity at each hierarchical level of the homeostatic (autonomic, or emotional motor [69]) system. The opposite effects of morphine on COLD and HPC cells are illustrative. At the spinal level, the activity of COLD and HPC lamina I cells is probably related to the activation of cutaneous and deep vasoconstrictor sympathetic efferents, respectively, which are organized in an opponent fashion at spinal and brainstem levels [10,45]. For example, cold-induced activation of adrenal catecholamine release parallels the HPC-minus-COLD response function calculated for the thermal grill [79,83].

Conceptually, lamina I has a fundamental role in

distributing modality-selective afferent information related to the physiologic condition of the tissues of the body, so it is integrally involved with homeostasis [33,35]. This concept is based on the observations that lamina I has strong projections to the sympathetic preganglionic nuclei in the spinal cord and to nearly all preautonomic and homeostatic sites in the brainstem, including the catecholamine cell columns, parabrachial nucleus, and periaqueductal gray, and that it receives descending inputs from the same preautonomic sites that project to the sympathetic nuclei, including the hypothalamic paraventricular nucleus (the "master autonomic control center"). Notably, the brainstem homeostatic sites that receive lamina I input also receive descending input from insular cortex.

From this global perspective, the lateral cortical target of lamina I projections (insula) may be viewed as a limbic sensory cortex [94], involved in the descending control of integrative autonomic function, in parallel with the parasympathetic afferent projection pathway (solitarius–parabrachial–VMb–rostral dorsal insula). The medial cortical target of lamina I projections (anterior cingulate) may be viewed as a limbic motor cortex (part of the emotional motor system [69]), involved in the motivational (affect, urgency) and behavioral (survival response) aspects of homeostasis and the care of the body. Interestingly, the sensation of itch also involves activation of anterior cingulate cortex [71] and can similarly be inhibited by cold or by noxious stimuli [110]. Succinctly stated, the function of COLD inhibition of HPC activity in the medial pathway might be to generate the contrasting sensation of burning pain that differentiates noxious cold from innocuous cool and motivates the appropriate integrated homeostatic and protective (ie, thermoregulatory) behavior.

Believing that COLD inhibition of polymodal nociceptive activity at thalamocortical levels reflects this general homeostatic opponent organization, I conjecture that the deep, burning ache experienced by many central pain patients may be related to dysfunctional regional cardiovascular regulation. Without cortical control, this could create a positive feedback cycle between decreased deep blood flow and increased HPC/deep vasoconstrictor activity that is subject to emotional variability. Moreover, because homeostasis at forebrain levels involves the whole body, the dysfunction would also reflect an imbalance in bilateral integration. Such bilateral integration would help explain cases of central pain in cases with spinal hemisection, Wallenberg's syndrome, or a hemithalamus [12,54,98], and would be relevant to pain localization in callosotomized patients [113]. Individual differences in homeostatic integration and control may also be pertinent to the selective appearance of central pain in a subpopulation of patients. Clinicians have repeatedly noted vague autonomic disturbances in central pain patients [12,66,96], and Bowsher [15] has recently provided quantitative evidence. Interestingly, Head and Holmes explicitly noted that more than two thirds of their thalamic pain patients experienced relief simply by going into a warm room. Today, it is said that central pain patients often obtain relief by exercise or by sitting in a spa. The effects of warming the skin, which would affect cold-evoked cutaneous HPC activity unilaterally, or warming the core, which would affect blood flow and deep HPC activity bilaterally (or the effects of different pharmacologic vasodilators), should be directly examined.

Finally, it should be emphasized that of the many interrelated goals of homeostasis, integrated thermoregulation is a primary function in mammals. Thermoregulation is not simply an autonomic function, but like physical trauma or itch, it also motivates appropriate behaviors that are necessary for survival. When endothermic mammals are cold, they are *motivated* to seek warmth. Such motivation involves strong affect, and when the cold is immediate and life threatening, it produces homeostatic (thermoregulatory) distress and a sensation of burning or stinging pain.

To my mind, the most fascinating characteristic of the affect generated by thermal sensation is its dependence on homeostatic needs. The pleasantness or unpleasantness of a given thermal stimulus depends directly on whole body or core temperature, whereas the discriminative sensation does not [95]. A cold stimulus that is pleasant if the body is overly warm is unpleasant if the body is cold. Thus, the affect generated by a temperature signal is governed by thermoregulatory integration. The sensory stimulus may be activating the same pathways in the brain, but the outcome has a different affective valence!

Thermoregulation involves spatial and temporal summation, but most importantly bilateral integration, such as has been observed physiologically in MDvc. Little is known about thermoregulatory integration in the forebrain, but it seems probable that it involves a broad network of loci involved in homeostasis, including the hypothalamus, amygdala, and periaqueductal gray, all of which are limbic (emotional motor) structures that are interconnected with the anterior cingulate, the insula, and MD. Even though the present data seem to indicate that activity in MDvc and the anterior cingulate is critical for deep, burning pain, I believe we should expect that the neural imbalance underlying central pain syndromes involves the entire homeostatic forebrain network. To point to area 24c or to the periaqueductal gray and say "here's the pain," for example, would be to ignore the global role of the homeostatic emotional motor system.

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