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Hypothalamic and Midbrain Circuitry That Distinguishes Between Escapable and Inescapable Pain

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Characteristics of emotional, behavioral, and physiological responses to pain are determined to a large extent by the behavioral significance of the pain, in particular to the degree to which the pain can be escaped. This review presents evidence that these different patterns of response depend on the activation of distinct pathways within the brain.

The emotional, behavioral, and physiological responses to picking up a hot plate are very different from the responses to pain arising from internal organs such as the gut. The reaction to grasping a hot plate is instantly to let go, that is to actively escape the pain. This action demands sudden muscular activity that is enabled by increases in blood pressure and redistribution of blood flow to muscles. On the other hand, an individual cannot escape the pain arising from the gut; this is an inescapable pain, generally accompanied by decreases in blood pressure and heart rate. These changes in cardiovascular functions evoked by the painful stimulus contribute to protective behavioral and physiological responses that enable an individual to avoid, escape, or cope with the pain.

Actual or potential tissue damage results in an experience of pain that includes both sensory and affective components. The first stage in this process is the activation of peripheral nerve fibers (C- and A\textsuperscript{\textdagger}) that terminate predominantly in superficial regions of the spinal dorsal horn (laminae I and II). These inputs feed into central circuits, some of which subserve the sensoridiscriminative aspects of the pain message and others that mediate the somatomotor, autonomic, neuroendocrine, and emotional components (i.e., the affective aspects).

Some autonomic adjustments evoked by nociceptive inputs are coordinated at the spinal level, and direct projections from neurons in lamina I to spinal regions containing neurons that regulate vascular tone (4) are good candidates to mediate these effects. However, in addition to spinal reflexes, it is clear that a number of structures in the brain coordinate protective responses to nociceptor stimulation, in which changes in autonomic outflow are but one component. Indeed, as predicted by Thomas Lewis in 1942 (7), it is likely that distinct central pathways provide the anatomic framework for mediating different patterns of autonomic change that are evoked by pain arising from different peripheral tissues, such as those from the skin or the gut.

Anatomic and electrophysiological evidence now supports Lewis' speculations, revealing as it does that many autonomic control centers in the brain stem receive direct and indirect nociceptive inputs that arise predominantly from neurons in lamina I of the spinal dorsal horn (e.g., see symposium proceedings by Gauriau and Bernard, Keay and Bandler, Lima, Albino-Teixeira and Tavares, Lumb, and Todd; introduced in Ref. 9). One approach in particular, the induction and localization of Fos (the nuclear protein product of the immediate early gene c-fos) as a marker of neuronal activation, has provided detailed information about the organization of pathways within the brain that are activated by noxious stimulation. The resolution of this technique has enabled subtle as well as found differences to be identified in the pattern of central neuronal activation following noxious stimulation of different structures, of noxious stimuli of different time courses, or of activation of different classes of peripheral nociceptors (C- and A\textdagger,-nociceptors).

In this review I will focus on recent findings about the organization of nociceptive inputs into just two of the brain regions that mediate autonomic responses to noxious stimuli. One of these is the periaqueductal grey (PAG), which is located in the midbrain, and the other is the hypothalamus, which is situated more rostrally in the brain. Evidence will be presented to support the view that separate circuits within the PAG itself, and also distinct pathways from the hypothalamus to the PAG, are activated by different classes of nociceptors (C- and A\textdagger,-nociceptors). The notion that these highly organized central circuits coordinate distinct patterns of autonomic response that are determined by the behavioral significance of the nociceptor input will be considered, bearing in mind that different qualities of the pain signal that are conveyed in C- and A\textdagger,-nociceptors.

Midbrain circuitry that distinguishes between escapable and inescapable pain

Columnar organization of the PAG: a role in active and passive coping strategies. A good starting point is to consider the functional organization of the PAG. The PAG is organized into a number of longitudinal columns that run parallel to the aqueduct, and a great deal is known of the consequences of activation of descending systems that emanate from them (e.g., Refs. 1, 2, and 8). Neurons in the dorsolateral and lateral columns are believed to coordinate active coping strategies that operate in emergency situations that are escapable. Such strategies include reduced responsiveness to noxious stimuli (antinociception), sympathoexcitation, and increased motor activity (i.e., fight-or-flight responses). In marked contrast, neurons in the ventrolateral column are believed to coordinate...
passive coping strategies that include antinociception accompanied by sympathoinhibition and hyporeactive immobility. One view is that this latter pattern of activity may operate during recuperation, after intense exercise, or in response to chronic pain when the stressor is inescapable (but see Ref. 15).

**Columnar organization of the PAG: nociceptive inputs from skin and viscera.** The patterns of autonomic and somatomotor activity evoked from the lateral and ventrolateral columns of the PAG resemble affective responses to pain arising from cutaneous structures and from deep somatic and visceral tissues, respectively (7). This observation led to the proposal, for which there is now considerable supporting evidence, that brief cutaneous insults activate the dorsolateral/lateral columns that coordinate active coping strategies, whereas nociceptive inputs from deep structures (such as muscle and viscera) drive neurons in the ventrolateral columns that coordinate passive emotional coping (e.g., Ref. 1). As such, these circuits are thought to mediate responses that are appropriate to meet the demands imposed by the particular environmental challenge, the former being escapable and the latter inescapable.

**Columnar organization of the PAG: inputs from C- and Aδ-nociceptors.** Recently, my colleagues and I have been investigating an alternative interpretation of the separation in central circuits activated from deep vs. superficial structures, which relies on the relatively high proportion of C-fibers in visceral nerves compared with cutaneous nerves (3). As a consequence, differential activation of the lateral and ventrolateral columns of the PAG might be more directly related to the relative proportions of C- and Aδ-nociceptors activated, rather than the locations of their terminals in deep vs. superficial tissues. This proposal has important implications with regard to the behavioral significance of the afferent input, because C- and Aδ-nociceptors convey different qualities of the pain signal; Aδ-nociceptors convey the escapable, pricking, well-localized sensations of first pain and C-nociceptors convey the burning, poorly localized sensations of second pain that are sometimes described as unbearable (13). The characteristics of Aδ- and C-fiber-mediated pain may be considered to endow escapable and inescapable qualities, respectively. These two fiber types are also believed to have different roles in the development and maintenance of chronic pain states (14).

The potential significance of this issue led us to develop a noninvasive technique, as first described by Yeomans and colleagues (20), whereby we could reliably and reproducibly activate preferentially either C- or Aδ-nociceptors. Slow heating rates (2.5°C/s) applied to a hindpaw dorsum were used to activate capsaicin-sensitive heat nociceptors, and higher rates (7.5°C/s) of heating applied to the same cutaneous fields were used to activate a population of heat nociceptors that were capsaicin insensitive. The vanilloid receptor VR-1, through which capsaicin exerts its effects, is expressed predominantly on C-nociceptors, and, as such, afferents activated by slow rates of heating were presumed to be largely C-fibers and those activated by fast rates largely Aδ-fibers. Using this approach combined with the induction of Fos protein as a marker of neuronal activation, we were then able to determine the precise organization of neuronal circuits engaged by activation of the different classes of nociceptors.

In individual animals, either slow or fast rates of skin heating were applied to the same area of skin on the hindpaw dorsum. Despite the stimuli being applied to identical locations on the paw, this led to marked differences in the columnar distributions of activated neurons in the PAG; slow rates of skin heating labeled significantly more neurons in the ventrolateral PAG, and fast rates resulted in higher numbers of activated cells in the lateral columns than in any other sector of the PAG (see Fig. 1). The results of these studies support the view that neurons in the ventrolateral PAG are indeed a focus of cutaneous C-fiber inputs. As such, the apparent targeting of visceral inputs onto neurons in the ventrolateral PAG may instead reflect the high proportion of C-fibers in visceral afferent nerves, rather than their anatomic organ of origin.

In other, complementary studies (10) we have established

![FIGURE 1. Photomicrographs of the distributions of Fos-positive neurons in the periaqueductal grey (PAG) following slow (2.5°C/s) and fast (7.5°C/s) rates of skin heating of the contralateral hindpaw. The black dots are the immunostained nuclei of Fos-positive neurons. Aq, Aqueduct. Reproduced with permission from Ref. 10.](Image)
that C-fiber input to the ventrolateral PAG is mediated, at least in part, after a single relay in the superficial dorsal horn. The design of these experiments, which are carried out in two stages, is shown in Fig. 2A. In the first stage, the PAG was “mapped” in anesthetized rats by monitoring the effects of microinjections of an excitatory amino acid (DL-homocysteic acid; DLH) on arterial blood pressure. Once a depressor site was localized in this way, a retrograde tracer (choleratoxin subunit b; CTb) was microinjected at the same site. The animals were then allowed to recover from anesthesia and, after several days to allow time for transport of CTb to the spinal cord, were reanesthetized before entering the second stage of the experiment, in which slow rates of skin heating were applied to the hindpaw dorsum to evoke Fos protein in dorsal horn neurons. Subsequent analysis of immunologically processed material enabled the laminar localization of single- and double-labeled neurons in the dorsal horn to be determined.

The vast majority of Fos-positive neurons (i.e., those activated by C-nociceptor stimulation) were located in laminae I and II of the superficial dorsal horn. A significant proportion of lamina I neurons were double-labeled with retrograde tracer from depressor sites in the PAG. In contrast, no neurons in lamina II were labeled retrogradely (Fig. 2B). Given the small area of skin stimulated (5 mm in diameter) together with the limited spread of retrograde tracer in the PAG (~500 μm in diameter), the number of lamina I neurons double-labeled in these experiments is almost certainly an underestimate of the total number of PAG projection neurons that are activated by C-nociceptors. Taking these factors into account, our data provide evidence for a substantial C-nociceptive input to the ventrolateral PAG that arises from lamina I of the spinal dorsal horn. An interesting, but as yet unexplained, observation was the high incidence of C-nociceptor-driven neurons in the lateral spinal nucleus that projected to the ventrolateral PAG (and see Ref. 6).

Columnar organization of the PAG: escapable and inescapable nociceptive inputs. The significance of our recent findings most likely resides in the functional properties of C- and Aδ-nociceptors. From a behavioral perspective, differences in the quality of the nociceptive messages conveyed by either C- or Aδ-nociceptors (13), together with their different roles in chronic pain (14), suggest that they may contribute, respectively, to the inescapable and the escapable components of the pain signal. As such, the inputs to the different functional columns of the PAG we have described may reflect their behavioral significance rather than their organ of origin. This view is supported by recent studies by Bandler, Keay, and colleagues which conclude that persistent, inescapable stimulation of cutaneous structures activates neurons in the ventrolateral PAG. In contrast, these authors found that escapable nociceptive inputs, such as brief insults to the skin, are more likely to activate neurons in the lateral columns (see Refs. 1 and 6).

Together, these data support the notion that inescapable nociceptive inputs, whether of deep or superficial origin, activate neurons in the ventrolateral PAG that coordinate appropriate patterns of autonomic and motor support, namely qui-
escence and sympathoinhibition. Escapable pain, on the other hand, would target the lateral columns and trigger patterns of autonomic, motor, and sensory changes that enable an animal to escape or confront a transient threat.

Hypothalamic-to-midbrain pathways that distinguish between escapable and inescapable pain

For many years, work in this laboratory has investigated the mechanisms and the descending pathways that mediate the antinociception that can be evoked from the hypothalamus. Our studies to date support the view that neurons within restricted areas of the hypothalamus exert coordinated effects on sensory processing and autonomic functions after engaging the control systems described above to originate in the different functional columns of the PAG. More recently, we have turned our attention to the stimuli that activate this hypothalamic-PAG axis.

Hypothalamic-PAG axis: a role in active and passive coping strategies? The hypothalamus has an undisputed role in the regulation of the cardiovascular system, and its widespread connections within the central nervous system place it in an unrivaled position for the integration of these controls with changes in other physiological variables in different emotional states and in response to different challenges in the external and internal environments. The effects of hypothalamic activation are diverse. However, of relevance to the current topic, distinctive patterns of change in sensory and autonomic functions similar to those coordinated by neurons in the PAG can be evoked from circumscribed regions of the hypothalamus. For instance, neuronal activation in one very restricted region evokes profound inhibition of spinal nociceptive reflexes that is always accompanied by sympathoexcitatory responses that include increases in arterial blood pressure (11). In the rat, this region corresponds to the lateral area of the anterior hypothalamus and shows considerable overlap with the “hypothalamic attack area” as described by Siegal and colleagues (18). In this region, and adjacent to it, other sites have been identified from which significantly less intense effects on nociceptive processing are accompanied by sympathoinhibitory responses that include decreases in arterial blood pressure (11).

The hypothalamus is a major source of afferent input to the midbrain, and the opposing cardiovascular effects evoked from different sites in the anterior hypothalamus are most likely mediated after engaging descending control systems that originate in the different columns of the PAG (e.g., Ref. 18). In support of this, functional anatomic studies in this laboratory have revealed that neurons at depressor sites in the anterior hypothalamus engage descending systems originating in the ventrolateral PAG (17). I shall now go on to describe some of our recent work, in which we have investigated the hypothesis that distinct hypothalamic-to-midbrain circuits are activated by nociceptive inputs of different behavioral significance.

Hypothalamic-PAG axis: organization of nociceptive inputs from skin and viscera. Reports of extensive direct, and indirect, inputs to the rostral hypothalamus from nociceptive spinal cord neurons (e.g., Ref. 5) suggest that descending control systems originating in the rostral hypothalamus may be activated by nociceptive stimuli in a similar way to those emanating from the different columns of the PAG.

With respect to the peripheral inputs to the proposed sympathoinhibitory hypothalamic-midbrain axis, initial studies (19) indicated that visceroresponsive neurons in the hypothalamus project to the ventrolateral PAG rather than to its lateral or dorsolateral sector. In contrast, fewer anterior hypothalamic neurons that are activated by noxious somatic stimuli project to the PAG, and those that do project almost exclusively to its dorsolateral/lateral sector (16). It would seem therefore that hypothalamic-midbrain projection neurons activated by noxious visceral or noxious somatic stimuli constitute largely separate populations of cells that innervate the ventrolateral or dorsolateral/lateral columns of the PAG, respectively. Functional anatomic studies suggest that the descending projections from the anterior hypothalamus to the PAG are, at least in part, excitatory (17). As such, activity in this highly organized hypothalamic-midbrain circuitry could act to reinforce active or passive coping strategies that are coordinated by neurons in the PAG in response to pain arising from visceral or resulting from cutaneous insults.

Hypothalamic-PAG axis: organization of nociceptive input from C- and Aδ-nociceptors. Recent (12) and ongoing studies are designed to investigate whether the apparent functional organization in the descending projections from the hypothalamus to the different columns of the PAG extends to circuits engaged by different components of the nociceptive message that arise from the same peripheral tissue. In other words, the hypothalamic-midbrain axis appropriately organized to constitute part of the central representation of escapable and inescapable pain, as defined by its pattern of activation by C- or Aδ-nociceptors? Using slow rates of skin heating, the studies have demonstrated that neurons driven by C-fiber activation are widely distributed in the rostral hypothalamus. However, the subpopulation of these neurons that project to the dorsolateral/lateral column.
the PAG were focused in the lateral area of the anterior hypothalamus and projected predominantly to the ventrolateral sector of the PAG.

A striking feature of these recent data is that, when compared with results of our earlier study (19), neurons driven by pinch, or by slow rates of heating, of the same peripheral locus (in this case the hindpaw) had very similar distributions throughout the rostral hypothalamus. However, they differed markedly with respect to their projection targets in the PAG; neurons activated by slow rates of skin heating projected predominantly to the ventrolateral sector, and those driven by pinch stimuli projected to the dorsolateral/lateral sector. That both of these stimuli were brief, were somatic, and were applied to the same structures in the periphery provides strong evidence that the differences in the descending projection targets of hypothalamic neurons that they activate is determined by the profile of afferent fibers that convey the different nociceptive messages to the central nervous system. In this respect, the slow rate of skin heating would have preferentially activated Aδ- and C-nociceptors, whereas the pinch stimulus would have activated both Aδ- and C-nociceptors. The question of whether or not hypothalamic neurons activated by fast rates of skin heating project preferentially to the dorsolateral/lateral columns of the PAG remains to be determined.

Hypothalamic-PAG axis: the anatomic substrate for fine-tuning responses to escapable and inescapable pain? The distributions and interconnections of hypothalamic and midbrain neurons activated by superficial and by deep nociceptors, and by C- compared with Aδ-nociceptors, have revealed neuronal circuitry that can distinguish between escapable and inescapable pain. Highly organized projections have been described from other forebrain centers, such as the prefrontal cortex and amygdala, to discrete columns of the PAG (for review, see Ref. 1). It is postulated that this arrangement allows for the complex behaviors integrated by the PAG to be modulated by higher centers. Our own studies have now revealed that projections from the hypothalamus to the different columns of the PAG also show a high degree of functional organization and have provided important insights into their possible roles in mediating affective responses to different components of the pain signal. More specifically, hypothalamic neurons activated by brief, escapable, somatic stimuli (such as pinch) target the dorsolateral/lateral sector and, in contrast, neurons driven by cutaneous C-fibers or by inescapable noxious visceral stimuli project more heavily to the ventrolateral sector (Fig. 3). Together, these data support the notion that the central representation of escapable vs. inescapable pain is indeed reflected in the organization of projections from the rostral hypothalamus to the PAG. This raises the possibility that distinct populations of hypothalamic neurons may, under certain circumstances, modulate the functioning of the different columns of the PAG. The full pattern of active and passive coping behaviors can be evoked in decerebrate animals. However, inputs from higher centers, including the hypothalamus, may provide a more processed modulatory input that fine-focuses the expression of active and passive coping strategies that are driven by nociceptive inputs of different behavioral significance.

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