Pathobiology of Visceral Pain: Molecular Mechanisms and Therapeutic Implications
V. Central nervous system processing of somatic and visceral sensory signals

URI LADABAUM,1 SATOSHI MINOSHIMA,2 AND CHUNG OWYANG3
1Division of Gastroenterology, Department of Medicine, University of California, San Francisco, California 94143-0538; and Divisions of 2Nuclear Medicine and 3Gastroenterology, Department of Medicine, University of Michigan, Ann Arbor, Michigan 48109-0362

Ladabaum, Uri, Satoshi Minoshima, and Chung Ow- yang. Pathobiology of Visceral Pain: Molecular Mechanisms and Therapeutic Implications. V. Central nervous system processing of somatic and visceral sensory signals. Am J Physiol Gastrointest Liver Physiol 279: G1–G6, 2000.—Somatic and visceral sensation, including pain perception, can be studied noninvasively in humans with functional brain imaging techniques. Positron emission tomography and functional magnetic resonance imaging have identified a series of cerebral regions involved in the processing of somatic pain, including the anterior cingulate, insular, prefrontal, inferior parietal, primary and secondary somatosensory, and primary motor and premotor cortices, the thalamus, hypothalamus, brain stem, and cerebellum. Experimental evidence supports possible specific roles for individual structures in processing the various dimensions of pain, such as encoding of affect in the anterior cingulate cortex. Visceral sensation has been examined in the setting of myocardial ischemia, distension of hollow viscera, and esophageal acidification. Although knowledge regarding somatic sensation is more extensive than the information available for visceral sensation, important similarities have emerged between cerebral representations of somatic and visceral pain.

PET; fMRI; pain; brain; perception

SOMATIC AND VISCERAL SENSORY signals relay information from an organism's external and internal environment and make essential contributions to homeostasis and behavior. Among sensory experiences, pain may carry particular significance for survival. Until recently, knowledge of the central nervous system substrate underlying somatic and visceral sensation relied on animal studies, pathological lesions and neurosurgical interventions in humans, and human psychophysical and electrophysiological studies. In the last decade, noninvasive functional brain imaging techniques have contributed greatly toward understanding the cortical and subcortical representation of somatic pain in humans under various experimental and pathological conditions and have opened a promising avenue of investigation into visceral sensation.

PAIN AS A MULTIDIMENSIONAL EXPERIENCE

Pain is recognized as a multidimensional experience including several coexisting components. The sensory-discriminative component refers to the experience of the unpleasant and emotional aspects of the pain. Finally, the cognitive-evaluative component consists of evaluation and interpretation of the meaning of the pain experience. Classically, a lateral pain system, including the lateral thalamic nuclei and somatosensory cortex, has been proposed to mediate the sensory-discriminative component of pain, whereas a medial pain system, including medial thalamic nuclei and the anterior cingulate and insular cortices, has been proposed to subserve its affective-motivational component.

FUNCTIONAL BRAIN IMAGING

Cerebral activation studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) exploit the fact that increased neuronal activity is associated with increases in regional
blood flow and oxygenated blood volume. Radiolabeled compounds with short half-life, most commonly $H_2^{18}O$ injected intravenously, are used in PET activation studies as markers of regional blood flow. A common fMRI technique detects changes in the regional oxygenation of hemoglobin resulting from changes in neuronal activity. Regions of activation may be identified by subtracting regional cerebral blood flow during a control condition from blood flow during a stimulus condition or by correlating regional blood flow with the intensity or time course of a stimulus or its perception. In activation studies, the major advantages of fMRI over PET are the lack of radiation exposure, allowing repeated studies in the same individual, and superior temporal resolution. PET imaging with radiolabeled pharmaceuticals and other ligands offers the ability to study receptor distribution and explore the site of action of therapeutic agents.

**CEREBRAL REPRESENTATION OF SOMATIC SENSATIONS**

Pioneering imaging studies challenged earlier contentions that the cerebral cortex plays a minimal role in pain perception. Phasic heat pain applied to the forearm produced contralateral activation in the anterior cingulate cortex (ACC) and primary somatosensory (SI) and secondary somatosensory (SII) cortices (23). Phasic heat pain applied to the hand led to activation in the contralateral ACC, thalamus, and lentiform nucleus (13). In both studies, blood flow measures during nonpainful heat were subtracted from measures with painful heat, thus minimizing signals relating to mechanical or painless thermal stimulation and emphasizing pain perception.

Additional studies provided greater detail regarding the cerebral representation of painful and painless somatic stimuli. Phasic heat to the forearm activated the contralateral SI, SII, anterior insula, ACC, two foci within the supplementary motor area, and thalamus; in contrast, vibrotactile stimulation activated the contralateral SI, bilateral SII, and posterior insula (6). An investigation including imaging of the posterior fossa confirmed previously reported sites of activation with noxious heat and demonstrated dorsal midbrain and cerebellar vermis activation (5). Furthermore, simple differences in thermal stimulus intensity did not reproduce the activations with heat pain, suggesting that the activated structures mediate the components of acute heat pain.

Numerous studies have since employed phasic or tonic heat pain and other stimulation paradigms, including minor dermal injury, cold pain, electrical stimulation, and vibrotactile stimulation. Despite some differences in results, which may relate to variability in methods and subjects, a group of structures has been identified that are activated during somatic pain (9). These structures include the ACC, insula, thalamus, SI, SII, motor and premotor cortices, prefrontal and inferior parietal cortices, lentiform nucleus, hypothalamus, periaqueductal gray (PAG) in the brain stem, and cerebellum (Fig. 1). The findings are consistent with the interpretation that SI displays somatotopic organization and participates in the sensory-discriminative component of acute pain perception. In contrast, the anterior insula, prefrontal cortex, and ACC appear to serve roles other than stimulus identification and localization (see below). Activity in the lentiform nucleus, motor and premotor cortices, and cerebellum may reflect motor planning in the context of constrained movement due to the imaging experiment. PAG activation may reflect its important role in descending modulation of spinal input to the brain. Activation of the hypothalamus and PAG has been interpreted as engagement of the brain defense system, because these structures, together with the amygdala, integrate autonomic responses to threatening stimuli.

The ACC is activated in nearly all pain studies and has been the focus of several directed investigations. Increases in blood flow in two regions of the ACC, the perigenual and midcingulate portions, were identified in response to heat pain (25). On the basis of subdivisions of the cingulate cortex derived from cytoarchitectural and neurobiological studies, these areas of activation were suggested to represent the affective component of pain, such as suffering, and response selection, respectively. The ACC, SI, SII, and insula were studied during innocuous and noxious hot and cold stimuli and the thermal grill illusion (7). The thermal grill illusion uses interlaced warm and cool bars to produce painful burning similar to that of intense cold. The thermal grill and painful cold both produced activation in the ACC, SII, and the middle/ anterior insula, whereas the cool component of the thermal grill activated only the insula and SII and the warm component activated the insula and SI. Therefore, the ACC activation was specific to the perception...
of thermal pain. In addition, all thermal stimuli activated the middle/anterior insula, supporting an important role for this region in pain and temperature sensation.

The ACC, SI, SII, and insula were again the subject of an investigation relying on hypnosis to differentiate pain affect from perception of intensity (19). Painful heat activated all four areas, as did painful heat after hypnotic induction but before suggestion of increased or decreased unpleasantness. Hypnotic suggestion selectively increased or decreased perception of pain unpleasantness but not intensity, and this effect was paralleled by changes only in ACC activation. This finding suggests that pain unpleasantness is encoded in the ACC, leading the authors to propose that the level of pain-evoked ACC activation is determinant in the reaction to pain. A recent study confirmed the correlation between unpleasantness and activity in the posterior ACC (24). Furthermore, pain intensity was correlated with activity in the periventricular gray and posterior cingulate cortex, and perception of the pain threshold (interpreted as a gating function) was related to activity in the ACC, frontal inferior cortex, and thalamus.

Because activation of cerebral structures in earlier studies could have reflected attention to the stimulus or anticipation and not the pain experience per se, subsequent investigations have been designed to separate attention and anticipation from the pain experience. Painful transcutaneous electrical nerve stimulation of the median nerve activated a small portion of the ACC, generally in the posterior part of Brodmann’s area 24 (8). In contrast, a silent word generation task produced activation in a larger region of the ACC, anterior and superior to the area activated with pain. A similar study employed painful heat and the Stroop interference task, in which incongruent color words (such as “red” written in blue ink) are presented to a subject who is instructed to name the ink color (10). Painful heat activated the perigenual and midcingulate portion of the ACC, whereas only the midcingulate portion showed activation with the Stroop task. Individual subject analysis revealed widespread and independent areas of activation in the ACC with the two tasks. Thus the activation of the ACC during the experience of pain cannot be explained solely on the basis of attention.

The dissociation of the pain experience from anticipation has been demonstrated in two elegant studies. Painful hot and nonpainful warm stimulation were applied preceding by different colored lights, which the subjects learned to identify as associated with either painful or warm stimulation (17). Pain activated the caudal ACC, middle insula, and anterior cerebellum. The anticipation of pain, defined as brain activation during the light preceding pain compared with the light preceding warmth, produced activation from the perigenual ACC to the frontal pole, the anterior insula, and the posterior cerebellum. Notably, activation in the regions associated with pain was consistent in all trials, whereas it increased over trials in the regions associated with anticipation, reflecting the learning process on the relationship between light color and stimulus. Thus anticipation activated distinct cerebral regions in close proximity to those activated by pain. A second study examined the ACC, ventromedial prefrontal cortex, and PAG during the anticipation of an unpredictable painful injection or a predictable painful electrical stimulus (12). Anticipation of the unpredictable stimulus activated the caudal ACC, two regions in the medial prefrontal cortex, and the PAG. Anticipation of the predictable stimulus, during which subjects reported using imagination strategy to distract from the pain, resulted in decreases in blood flow in the caudal ACC and the ventromedial prefrontal cortex. These findings were interpreted to represent vigilance to the unpredictable stimulus and distraction with the predictable stimulus. Because subjects were right-handed and right-sided cerebral preponderance to anticipation was observed, the authors support a hypothesis of preferential involvement of the nondominant hemisphere in emotional arousal.

Temporal analyses of the fMRI signal have recently yielded important insight into somatic pain perception. Responses to subcutaneous ascorbic acid injection, monitored over ~20 min, revealed positive correlation with pain intensity in SI, ACC, and posterior cingulate, premotor, and motor cortices (18). Negative correlation was observed in medial parietal, medial prefrontal, and posterior and perigenual cingulate areas. This study demonstrated a direct link between the time course of pain intensity perception and activation in discrete cerebral regions. To differentiate stimulus identification from pain perception, cerebral blood flow in the middle third of the contralateral brain was monitored during phasic heat pain (1). Pain perception was shown to increase for the duration of steady stimulus application, with some habituation in initial trials followed by sensitization. Separate predictor functions reflecting the dissociation between stimulus application and pain perception were constructed, and the correlation was assessed between these functions and regional activation. Insular cortical activity best reflected the stimulus, consistent with a role in encoding temperature characteristics. Activation in more posterior regions of the parietal cortex was more highly correlated with pain perception than in more anterior regions. On the basis of animal studies, clinical observations, and the results of this study, the authors concluded that the posterior parietal cortex may function in the conscious perception of pain.

Functional brain imaging in clinical conditions of somatic pain is illustrated by a study on chronic neuropathic pain. Patients with chronic painful mononeuropathy were studied before and after successful nerve block (11). Compared with the pain-alleviated state, the ongoing pain state was associated with activation bilaterally in the anterior insula, the posterior parietal, prefrontal and posterior cingulate cortices, the cerebellar vermis, and the posterior sector of the right ACC (Brodmann’s area 24) regardless of the laterality of the mononeuropathy. Reduction in blood flow was
detected in the contralateral posterior thalamus, and no changes were seen in SI or SII. Thus, compared with experimental acute pain, chronic pain appears to activate preferentially those regions associated with the affective-motivational rather than the sensory-discriminative dimension of pain, with apparent non-dominant hemispheric lateralization of ACC activity.

Mechanical hyperalgesia, or pain in response to normally innocuous tactile stimuli, is a common feature of neuropathic pain syndromes. Recently, capsaicin-induced mechanical hyperalgesia was shown to produce higher activation in the contralateral prefrontal cortex than the same mechanical stimulation without capsaicin (4).

To explore pain responses in a chronic pain condition involving inflammation and a chronic pain condition in which no tissue injury can be readily identified, painful heat stimulation individualized to each subject was studied in patients with rheumatoid arthritis and patients with atypical facial pain (14). The latter demonstrated lowered pain thresholds and increased scores for depression and anxiety. Compared with controls, patients with rheumatoid arthritis exhibited reduced responses in the ACC and prefrontal and cingulofrontal transition cortices. In contrast, patients with atypical facial pain demonstrated significantly greater ACC responses than controls. Chronic inflammatory pain, therefore, appears to affect the central processing of acute pain in quite a different way from chronic functional pain.

CEREBRAL REPRESENTATION OF ANGINA AND SILENT MYOCARDIAL ISCHEMIA

The first functional brain imaging study of visceral pain examined cerebral responses during dobutamine-induced angina pectoris in subjects with coronary artery disease (20). Dobutamine infusion produced typical chest pain as well as electrocardiographic changes reflective of myocardial ischemia. Compared with the rest state, cerebral blood flow increases during angina were seen in the hypothalamus and PAG, bilaterally in the thalamus and lateral prefrontal cortex, and in the left inferior anterocaudal portion of the ACC. Diminished blood flow was observed bilaterally in the microstrocaudal cingulate cortex and fusiform gyrus and right posterior cingulate and left parietal cortices. After dobutamine and following disappearance of angina and ischemic electrocardiographic changes, thalamic activation remained but no cortical activation was detectable. Thus there appears to be continued visceral afferent input to the thalamus from the heart after resolution of angina. These findings suggest that the thalamus may serve a gating role and that involvement of cortical structures is necessary for perception of pain from the heart.

These observations were extended in an investigation of nondiabetic patients with silent myocardial ischemia compared with patients with angina (21). Ischemia with electrocardiographic changes was again induced with dobutamine, but only the latter group experienced angina. Compared with the resting state, angina was associated with bilateral activation in the thalami and prefrontal, basal frontal, and ventral cingulate cortices. In contrast, silent myocardial ischemia led to bilateral thalamic activation and only right frontal cortical activation. Detection of thalamic activation in both states indicates that signals are transmitted from the heart to the brain during symptomatic as well as silent ischemia. Furthermore, the limited cortical activation with silent ischemia compared with angina suggests that abnormal central processing, and not peripheral nerve dysfunction, explains the absence of symptoms in this group of subjects with silent ischemia. On the basis of comparisons with cerebral activation patterns with somatic pain, the authors of these studies proposed that the ventral cingulate and frontal cortices can be considered the central projections of visceral pain, in contrast to the dorsal cingulate and somatosensory cortices with somatic pain.

CEREBRAL REPRESENTATION OF ENTERIC STIMULI

The hypothesis that altered visceral sensitivity may be an important determinant of symptoms in the functional gastrointestinal disorders has been a major impetus for research into visceral sensation, including the cerebral processing of enteric stimuli. The first investigation of cerebral activation during enteric visceral stimulation compared responses to painful rectal distension and its anticipation in healthy subjects and patients with irritable bowel syndrome (IBS), which is characterized by abdominal pain and altered defecation in the absence of structural or metabolic abnormalities (22). In response to actual or simulated rectal distension, normal subjects showed activation of the ACC, whereas IBS patients did not. In normal subjects, symptom intensity and regional activation were strongly correlated in the ACC but no other brain region. In contrast, ACC activity and symptom intensity were uncorrelated in patients with IBS. On the other hand, IBS patients showed activation of the left prefrontal cortex with anticipation of rectal distension, but this brain region was not activated in normal controls. The ACC displays high opiate receptor density, and its activation may include central pain inhibition; activation of the frontal lobes could reflect a vigilance network (22). These two cerebral regions appear to have reciprocal inhibitory connections. It is conceivable that the preferential activation of the prefrontal lobe without activation of the ACC in IBS patients represents a form of cerebral dysfunction associated with heightened perception of visceral pain.

A recent study has expanded the available information on the cerebral representation of rectal pain in healthy subjects (3). During rectal balloon inflation eliciting discomfort, regional activation was observed in the insula, ACC, inferior parietal lobule, SI, and in the prefrontal, motor, posterior cingulate, and visual cortices. These results demonstrate important similarities with the cerebral activation patterns observed in studies of somatic pain.
The cerebral structures activated by esophageal distension have also been investigated (2). Painless but perceived distal esophageal distension was associated with bilateral activation in the insula, along the central sulcus, and the frontal/parietal operculum. Painful distension elicited more intense activation in these areas as well as additional activation in the right anterior insula and the ACC. Such activation of the anterior insula and the ACC with a painful but not with a painless mechanical visceral stimulus is analogous to findings with somatic stimulation.

Esophageal symptoms are frequently elicited by gastric acid reflux, but there is an imperfect relationship between symptoms and the degree of esophageal mucosal acid exposure. Motivated by this observation, a study was designed to assess cerebral responses to esophageal stimulation by distension as well as acidification in healthy volunteers (15). Painless balloon distension elicited activation in the prefrontal cortex near the ACC, the insula, the parietal operculum, and the parietooccipital cortex near the posterior cingulate cortex. Acid perfusion produced a feeling of coolness or awareness of fluid but no pain or heartburn, and the same symptoms were experienced during control saline perfusion. Saline produced no detectable cerebral activation, but acid perfusion led to characteristic activations concentrated in the posterior cingulate, parietal, and anteromesial frontal lobes. For individual subjects, the regions activated by distension and acidification were similar. Activation latency for the mechanical stimulus was ~5 s and for acidification was ~5 min. Distension after acidification demonstrated a prolonged activation latency of ~10 s. Thus cerebral activation is detectable after esophageal mucosal acidification in the absence of heartburn or pain, and the regions activated are similar to those activated by mechanical distension but with significantly different time courses of activation.

Abnormalities in gastric sensation and intragastric meal distribution are believed to contribute to symptoms in functional dyspepsia. Distal gastric distension may elicit a sense of fullness or bloating, pain, and nausea. The cerebral representation of symptomatic distal gastric distension has recently been investigated in healthy subjects (16). Increases in distending pressure evoked progressive increases in bloating, pain, and nausea intensity. These were paralleled by progressive activation in a series of cerebral structures, including the thalamus, insula, ACC, caudate nucleus, and the cerebellar hemispheres and vermis. Due to the strong correlation among symptoms, activation of specific structures could not be assigned to the experience of individual symptoms.

CONCLUSION

Functional imaging techniques make possible the study of central nervous system activity associated with somatic and visceral sensation, including the experience of pain. The multidimensional experience of pain involves activity in a widely distributed set of cerebral regions. The specific contributions of individual structures to the perception of somatic pain are beginning to be dissected. Compared with somatic sensory research, exploration of the central processing of visceral sensation is in its early stages, but already important similarities to somatic sensation have emerged. Elucidation of the central mechanisms associated with pathological pain in various disorders may one day contribute to novel therapies in these challenging clinical conditions.

This work was supported by National Institutes of Health Grants SP30-DK-34933 (University of Michigan) and M01-RR-00079 to the University of California, San Francisco General Clinical Research Center, including a Clinical Associate Physician Award to U. Ladabaum.

REFERENCES


