# Mechanisms of Cardiac Pain

*Robert D. Foreman,*[*1] *Kennon M. Garrett,*[1] *and Robert W. Blair*[1]

## ABSTRACT

Angina pectoris is cardiac pain that typically is manifested as referred pain to the chest and upper left arm. Atypical pain to describe localization of the perception, generally experienced more by women, is referred to the back, neck, and/or jaw. This article summarizes the neurophysiological and pharmacological mechanisms for referred cardiac pain. Spinal cardiac afferent fibers mediate typical anginal pain via pathways from the spinal cord to the thalamus and ultimately cerebral cortex. Spinal neurotransmission involves substance P, glutamate, and transient receptor potential vanilloid-1 (TRPV1) receptors; release of neurokinins such as nuclear factor kappa b (NF-kb) in the spinal cord can modulate neurotransmission. Vagal cardiac afferent fibers likely mediate atypical anginal pain and contribute to cardiac ischemia without accompanying pain via relays through the nucleus of the solitary tract and the C1-C2 spinal segments. The psychological state of an individual can modulate cardiac nociception via pathways involving the amygdala. Descending pathways originating from nucleus raphe magnus and the pons also can modulate cardiac nociception. Sensory input from other visceral organs can mimic cardiac pain due to convergence of this input with cardiac input onto spinothalamic tract neurons. Reduction of converging nociceptive input from the gallbladder and gastrointestinal tract can diminish cardiac pain. Much work remains to be performed to discern the interactions among complex neural pathways that ultimately produce or do not produce the sensations associated with cardiac pain. © 2015 American Physiological Society. *Compr Physiol* 5:929-960, 2015.

## Introduction

Angina pectoris refers to discomfort or pain associated with an imbalance between myocardial oxygen supply and demand. Angina generally is due to a critical stenosis of an epicardial artery that produces an oxygen supply/demand imbalance that leads to myocardial ischemia. The typical cascade after the onset of myocardial ischemia is dysfunction of the left ventricle, changes in the electrocardiogram, and then the onset of pain in many but not all patients. Typical symptoms for the localization of pain, based on the common presentation in men, include a crushing, pressure, or squeezing sensation in the center of the chest that may or may not be described as pain. Pain commonly is referred to the left shoulder and flexor portion of the left arm, and less commonly to the right arm, neck, or jaw, or in the epigastric region (85, 143, 199). Recently, there has been an appreciation that women's experience of angina and therapeutic procedures is often different from men (140). This less common localization of angina, often described as "atypical" pain, is referred to the jaw, neck, shoulders, and back, and there may be no sensations from the chest. If there is sensation from the chest, it is not a crushing sensation (85, 88, 256). Instead, there is a fullness sensation or a sharp, stabbing, burning pain. Chest pain or discomfort, whether typical or atypical, is subjectively one of the most disconcerting and anxiety generating symptoms because it is often associated with potentially critical heart disease and with risk of death. Unfortunately, often in women and sometimes in men chest pain may be misinterpreted as being the result of indigestion. Thus, there is a great variability in the location of cardiac pain among different patients and with the associated subjective sensations (207). The association between ischemic heart disease and cardiac pain is important but episodes of transient myocardial ischemia can occur with the absence of pain.

The convergence projection theory, first proposed by Ruch (301), sought to explain how pain originating from a visceral organ could be referred to somatic structures. In essence, the theory states that visceral and somatic noxious sensory inputs converge onto a common pool of projection neurons, such as spinothalamic tract neurons, within the central nervous system (Fig. 1). Under normal circumstances, these neurons transmit noxious somatic input to higher centers where the input is interpreted as somatic pain. Noxious cardiac stimuli, such as angina, activate this same population of projection neurons, and the brain misinterprets the origin of the nociceptive signal as originating from the somatic structures, resulting in referred pain. One overall theme of this review is that convergence of visceral and somatic input occurs in a variety of brain regions, and these complex patterns of interactions of visceral and somatic information can lead to the varying experiences of sensations felt by patients with coronary artery disease.

*Correspondence to Robert-Foreman@ouhsc.edu

[1]Department of Physiology, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma, USA

Published online, April 2015 (*comprehensivephysiology.com*)

DOI: 10.1002/cphy.c140032

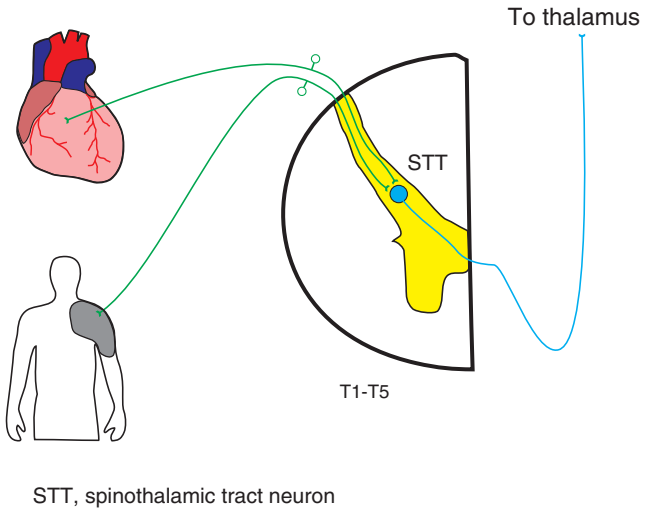



Figure 1 Viscerosomatic convergence onto upper thoracic spinothalamic tract neurons. Both cardiac sensory information and somatic sensory information from the chest and upper arm converge onto the same population of spinothalamic tract neurons in the upper thoracic (T1-T5) spinal dorsal horn segments. In this and all subsequent figures, green pathways are excitatory, and the recorded central neuron and its axon are colored blue.

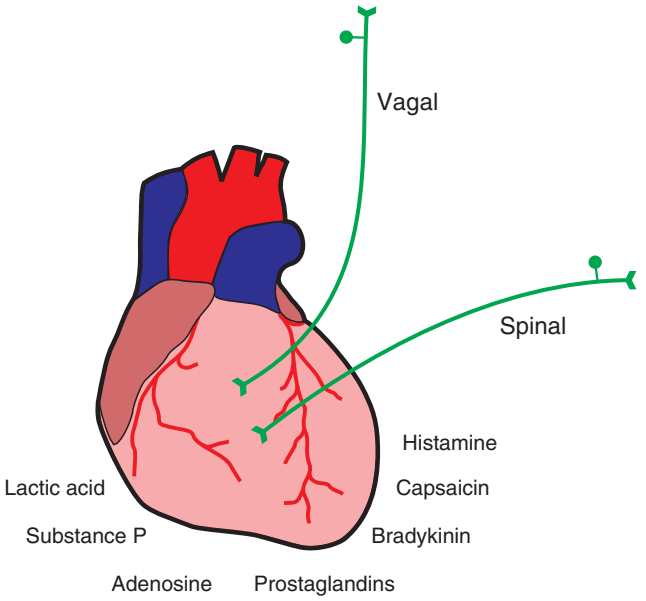



Figure 2 Mediators that activate and/or enhance sensitivity of cardiac afferent fibers. Each of the substances can affect both spinal and vagal afferent fibers.

The purpose of this article is to summarize research that has led to an understanding of possible neurophysiological mechanisms that explain the sensations associated with angina pectoris. We will start with cardiac afferents that mediate anginal sensations. Next, we will consider spinal and brain regions that contribute to cardiac nociceptive processing. Lastly, we will describe neural interactions between organs that can allow one organ to affect the function of another, as well as lead to misinterpretations (and misdiagnoses) of the origin of visceral disease because of similar clinical presentations. At the end of this presentation, it will be obvious that more research needs to be conducted to explain how the variety of anginal sensations occurs in different people.

## Spinal and Vagal Afferents

Angina pectoris often results from ischemic episodes that excite chemosensitive and mechanoreceptive receptors in the heart (see Refs. 74, 109, and 117 for review). Ischemic syndromes, particularly myocardial infarction and unstable angina, are commonly associated with fissures or erosions of atherosclerotic plaques that lead to release of several chemical mediators into the coronary artery lumen, platelet activation, and formation of a thrombus that can occlude coronary arteries and significantly reduce blood flow. All of these events cause the release of numerous chemical mediators, including serotonin, histamine, thromboxane A2, bradykinin, reactive oxygen species, especially hydroxyl radicals, lactic acid that releases protons, and adenosine which leads to the production of prostaglandins (PGE2 and PGI2) via a cyclooxygenase pathway (117), (Fig. 2). These chemical mediators either individually, or frequently in combination, interact with specific receptors most commonly on chemically sensitive terminals that lead to the depolarization of the cardiac visceral spinal afferent fibers.

### Spinal cardiac afferent fibers

Cardiac visceral afferent sensory fibers that terminate in the spinal cord have diffuse or compact unencapsulated terminals that are branched and found most commonly in the epicardium (179,226). However, the sensory endings do not appear to terminate in the myocardium; instead, a mixture of myelinated and unmyelinated fibers forms bundles that can be traced through the connective tissues of the septa between the muscles (226). Anatomical studies have shown that spinal cardiac afferent fibers primarily innervate the anterior portion of the left ventricle (273,274). This distribution is consistent with the observations that myocardial infarction of the anterior region more often elicits tachycardia and hypertension, responses that are more commonly associated with sympathetic reflex activation (228, 275, 362).

Cell bodies of the cardiac visceral spinal afferent fibers originating from the heart and coronary arteries are located in the dorsal root ganglia (DRG) of the T2-T6 spinal segments, but they can also extend as far away as the C8-T9 segments (186, 353). Axons of these DRG cells enter at the tract of Lissauer and terminate in the same segment or may ascend and descend a few segments before they penetrate into the spinal gray matter (186). These axons arch over the dorsal rim of the spinal gray matter to enter lamina I or travel along the lateral edge of the gray matter to terminate primarily

in laminae V, VII, and X before synapsing with cell bodies located in these regions of the spinal gray (58, 59, 61, 329).

Both chemosensitive nociceptors and mechanoreceptors innervate the epicardium. Excitation of these mostly polymodal afferent fibers elicits pain, activates protective reflexes, and regulates cardiac function (47, see Ref. 166). Mechanosensitive myelinated Aδ- and unmyelinated C-fibers respond briskly to low threshold stimulation that also includes weak responses to bradykinin as well as increases in blood pressure (20). Recordings from mechanosensitive endings show that there is a regular discharge pattern of action potentials with each cardiac cycle, and there is a vigorous and immediate response to gentle movement of a fine probe or bristle when it is applied to the receptive field (206). In contrast, chemosensitive endings do not display cardiac modulation and discharge irregularly and infrequently (53). Interestingly both types of fibers can respond to bradykinin; however, only the fibers with chemosensitive endings demonstrate sensitization with the application of prostaglandins, particularly PGE1, to the heart (20, 235). Mechanoreceptive endings are not considered to be involved with angina pectoris, because the responses of these mechanoreceptors are below the noxious threshold. In contrast, chemosensitive fibers are considered to be nociceptors because they respond to stimuli outside the physiological range and evoke pseudoaffective cardiovascular reflexes (235, 378). Thus, chemosensitive fibers are generally unresponsive to mechanical stimulation but respond vigorously to the release of algogenic chemicals during myocardial ischemia (235).

## Chemical mediators

Chemical mediators including acids, adenosine, bradykinin, capsaicin, histamine, potassium, prostaglandins, and substance P excite unmyelinated spinal cardiac afferent fibers when they are directly injected into the coronary arteries or applied to the epicardial surface of the heart (20, 72, 117, 198, 347-351). Among these chemicals, adenosine also has been shown to be a critical constituent that contributes to cardiac pain. Adenosine administered either to healthy volunteers or patients experiencing angina pectoris resulting from ischemic heart disease generates angina-like pain without any changes in the electrocardiogram, and the intensity of pain is dose dependent (331-334). One cautionary note is that Pan and Longhurst (247) have shown that adenosine in their animal model does not activate spinal cardiac afferent fibers.

An important component of chemical mediators is their ability not only to excite spinal cardiac afferent activity independently but they may also interact with each other to modify the sensitivity of their effects (117). Bradykinin and histamine are released simultaneously during brief episodes of myocardial ischemia (113, 181, 183). These mediators independently generate action potentials in cardiac spinal sensory afferent fibers (116, 345). In addition, recordings of action potentials from ischemically sensitive single cardiac afferents have shown that bradykinin, via a cyclooxygenase mechanism, sensitizes these afferents to stimulation with histamine (116). Thromboxane A2, a cyclooxygenase product, also is released during myocardial ischemia, and it interacts reciprocally with bradykinin and through these interactions promotes the actions of the other mediator (118).

Sensitization of nociceptors after injury or inflammation occurs when prostaglandins, leukotrienes, substance P, and other chemical mediators are released due to local tissue damage. In the heart, thrombosed coronary atherosclerotic plaques can rupture or erode, thereby activating platelets and releasing sensitizing chemicals that inflame adventitia of coronary arteries, activate silent nociceptors, and sensitize chemosensitive receptors (76, 106, 182, 354). The release of substances such as substance P may sensitize nociceptors to intensify the pain experience felt in patients who are infused with adenosine (120). Prostaglandins are lipid autacoids that are derived from arachidonic acid and generated by the metabolism of arachidonic acid via the action of the cyclooxygenase pathway. These lipid messengers are found in increasing concentrations in the plasma of patients suffering from unstable angina pectoris or with acute myocardial infarction (30, 145). Prostaglandins sensitize chemical receptors located on the endings of sensory fibers that result in increasing the magnitude of the response via an increase in the magnitude of spontaneous activity and/or decreasing the receptor threshold (103, 121). To examine the effects of prostaglandins on sensitization of cardiac sensory afferent fibers, recordings were made from single afferent fibers that showed increased activity to myocardial ischemia and bradykinin (345). Blockade of the cyclooxygenase pathway with indomethacin significantly decreased the evoked activity resulting from myocardial ischemia and application of bradykinin to the heart. For more detail regarding the interactions among chemical mediators, see the detailed review by Fu and Longhurst (117).

The onset of angina pectoris associated with myocardial ischemia may depend on the activation of the transient receptor potential vanilloid-1 (TRPV1) receptors. TRPV1 receptors may function as molecular sensors that contribute to the processing of cardiac nociceptive information in spinal neurons. This receptor is a molecular integrator of noxious stimuli that is specifically expressed in the plasma membrane of nociceptive afferent fibers and opens an important nonspecific cation channel that is activated by capsaicin (CAP), the pungent ingredient found in chili peppers (55, 251). This receptor and receptor channel complex can detect release of bradykinin, serotonin, and adenosine triphosphate, as well as respond to changes in pH, lipid metabolites, and heat that may occur with tissue ischemia (171, 251). TRPV1-expressing afferent nerves are distributed extensively on the epicardial surface of the rat ventricle (378). Epicardial application of CAP excites visceral spinal afferent fibers and produces sympathoexcitatory reflexes (251, 316, 378); TRPV1 antagonists eliminate these effects. Injections of CAP into the left atrium or pericardial sac also activate spinal and spinoreticular neurons that receive convergent input from the heart and somatic structures in cats (42) and rats (267). These results suggest that excitation of

TRPV1-containing visceral spinal afferent fibers mediate the algesic responses associated with angina.

## Chemical activation of spinal cardiac dorsal root ganglion cells

The spinal cardiac visceral afferent fibers transmit nociceptive afferent information that passes through the pseudounipolar cell bodies located in the DRG on its way to the terminals in the spinal gray matter. The focus of attention for processing nociceptive information has generally concentrated on the spinal neural networks, because it was assumed that DRG did not affect transmission of sensory information in processing of cardiac nociception. However, numerous studies in the pain literature have shown that changes in neurotransmitters, neuromodulators, and cytokines in the DRG can modify nociceptive information (see review, 169). The somata of spinal visceral afferent neurons as well as general somatic primary afferent neurons are located in DRG. These pseudounipolar neurons are surrounded with numerous non-neuronal cells including satellite cells, endothelial cells, fibroblasts, mast cells, resident endoneurial macrophages, and occasional lymphoctyes (200, 366). These non-neuronal cells are not static. Peripheral nerve lesions in adult rats lead to alterations in the DRG that include changes in neuropeptide expression (151, 160, 161), and satellite cell proliferation (164). Thus, the potential exists for non-neuronal elements in the DRG to affect cardiac nociceptive transmission to the spinal cord.

TRPV1 receptors and the cytokine tissue necrosis factor alpha (TNFα) may modulate nociceptive transmission in DRG cells. Administration of capsaicin activates TRPV1 receptors on a subpopulation of somatic DRG neurons. It should also be noted that these receptors are expressed throughout the entire afferent nerve (55, 202, 335). Studies using double labeling immunohistochemical techniques have shown that most of the unmyelinated C-fibers and approximately 30% of the small A-delta fibers express TRPV1 receptors (202). Zahner et al. (378) used immunofluorescence labeling to show that TRPV1 receptors are present on the small and medium sized cell bodies of the thoracic DRG as well as primarily near the epicardial surface of the heart of vehicle treated rats. Intraperitoneal injections of resiniferatoxin (RTX), a potent analogue of capsaicin, substantially reduced TRPV1 immunoreactivity of the DRG cells and mostly eliminated TRPV1 immunoreactivity in the epicardium (Fig. 3). The limiting factor of this study is that RTX was injected systemically, and was not limited to the heart. However, epicardial application of iodo-RTX, a highly specific antagonist of TRPV1 receptors, eliminated the capsaicin-induced sympathoexcitatory responses (378). This provides evidence that limiting injections of RTX to the epicardium might also reduce the TRPV1 receptors on cells of the thoracic DRG.

Cytokines are chemical messengers that cells of the immune system secrete to act on other cells to coordinate appropriate immune responses. They are comprised of a diverse array of interleukins, interferons, and growth factors. Among the myriad of cytokines, TNFα has been examined for its changes during myocardial ischemia, although information about its role is still limited. Among a multitude of functions, this cytokine is proinflammatory with multiple phenotypic functions that are involved in the development and maintenance of neuropathic and inflammatory pain (79, 165, 170, 172, 360). Satellite cells and macrophages are major sources of TNFα and other excitatory cytokines that contribute to neuropathic pain (304, 356). Under normal conditions TNFα does not have much effect on acute somatic nociceptive information being transmitted to the central nervous system. However, if there is the onset of inflammation or changes in peripheral somatic structures, then TNFα is activated to enhance the function of the DRG cells, thereby amplifying the signals that are transmitted centrally. For example, after peripheral nerve injury the expression of TNFα mRNA increased in DRG (232). The glial cells in the DRG synthesize and release TNFα, which can lead to the induction of allodynia and hyperalgesia (171). Based on this information Niu et al. (238) examined the role of TNFα in the DRG of the upper thoracic spinal segments by performing occlusions of the left anterior descending branch of the coronary artery. Measurements of TNFα were determined at 0.5, 1, 3, and 6 h of acute myocardial ischemia/infarction (Fig. 4). After occlusions were applied for various lengths of time the DRG of the upper thoracic segments were removed. Their results showed that expression of TNFα was increased significantly in small

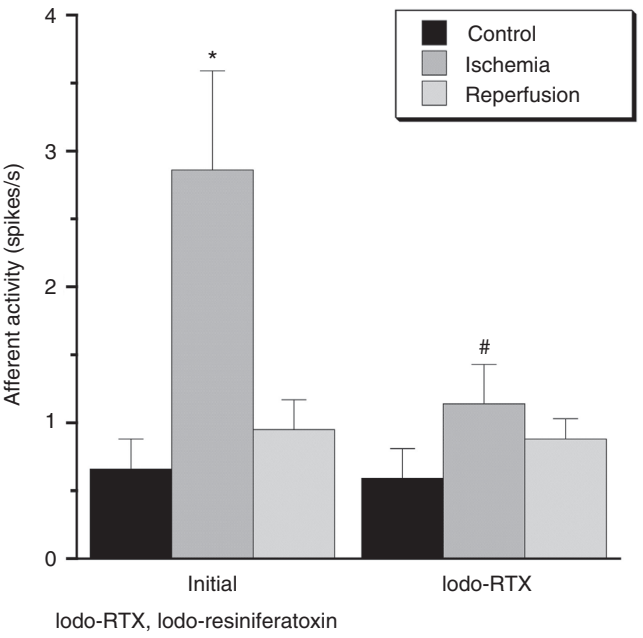



Figure 3 Effect of topical treatment with iodo-resiniferatoxin (iodo-RTX, 50 μmol/L) on mean response activity of cardiac afferents to 5 min of ischemia. Results indicate that iodo-RTX significantly reduced the responses of cardiac afferents to ischemia. Data are presented as mean ± SEM. $^{*}P < 0.05$ versus preischemia control; $\#P < 0.05$ versus afferent response to initial ischemia. (Adapted, with permission, from 251.)

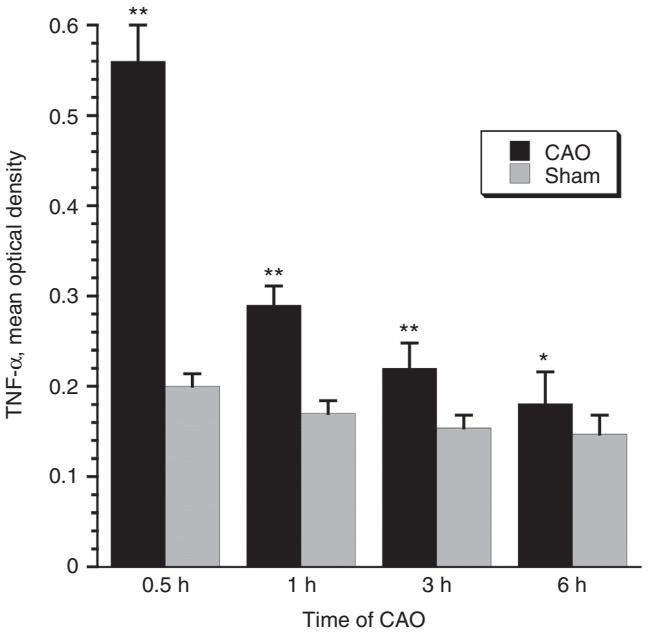



Figure 4 TNF-α in rat dorsal root ganglia. Closed bars represent mean optical density of immunoreactive material for TNF-α in the dorsal root ganglia of rats receiving coronary artery occlusion for 0.5, 1, 3, and 6 h. Hatched bars represent mean optical density of immunoreactive material for TNF-α in the dorsal root ganglia of rats 0.5, 1, 3, and 6 h following sham surgery. Results indicate that the expression of TNF-α in dorsal root ganglia was increased following coronary artery occlusion compared to sham. Data are presented as mean ± SEM. $^{**}P < 0.01$ versus sham; $^{*}P < 0.05$ versus sham. (Adapted, with permission, from 238.)

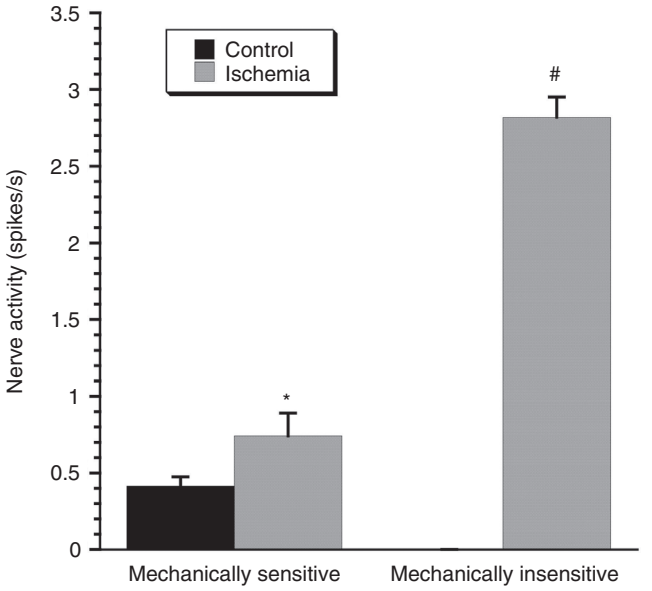



Figure 5 Comparison of the responses of mechanically sensitive and mechanically insensitive cardiac afferents to 5 min of myocardial ischemia. Results indicate that both types of cardiac afferents significantly increased their discharge rate in response to myocardial ischemia, but the responses of mechanically insensitive afferents were significantly more robust than the responses of mechanically sensitive afferents. Data are presented as mean ± SEM. $^{*}P < 0.05$ compared with control, $\#P < 0.05$ compared with the response of mechanically sensitive afferents to ischemia. (Adapted, with permission, from 250.)

and medium diameter neurons primarily during the shorter coronary occlusion time periods. Niu et al. (238) also noted that at the longer occlusion time periods, increased TNFα expression was found in the large diameter neurons, which usually do not participate in the transmission of nociceptive information. Their results also showed that the upregulation of TNFa mRNA was increased in small diameter DRG neurons and satellite cells. These results lead to the suggestion that TNFα is released during coronary artery occlusion, and the increased release of TNFα may amplify the number of action potentials that originate from the ischemic regions of the heart. As a result, the intensity of pain perception might be increased when the information reaches the areas of the brain that process and interpret the nociceptive information. Further research needs to be done to expand our understanding about the role of cytokines in the production of angina pectoris.

## Silent spinal cardiac afferent nociceptors

Silent nociceptors are also an important subcategory of receptors that may contribute to the afferent mechanisms associated with cardiac pain. The first clue that silent nociceptors may contribute to pain sensation resulted from the studies that examined silent afferent fibers in the knee joint, skin, and pelvic visceral organs of cats (135, 222, 312). These silent afferents most likely function as important nociceptors because they are unresponsive to physiological stimuli (59, 135, 223, 248). The results of previous studies raised the question of whether silent afferent fibers contribute to the pain associated with myocardial ischemia. Among the spinal sensory afferent fibers originating from the heart, only a subpopulation of these fibers are activated during myocardial ischemia (247, 249, 346), and numerous unmyelinated C-fibers do not respond to ischemic episodes (245, 247, 249, 348). To determine if these unresponsive C-fibers are silent nociceptors that respond to myocardial ischemia, Pan and Chen (250) used direct electrical stimulation of receptive fields on the surface of the heart to identify C-fibers that transmitted action potentials during the test stimulus but did not respond to mechanical stimulation of the receptive fields (Fig. 5). Using this technique, these investigators showed that there is a group of cardiac sensory afferent fibers that did not respond to mechanical stimulation of their receptive fields but discharged vigorously during myocardial ischemia resulting from coronary artery occlusion (250). In contrast to afferents that were responsive to mechanical stimulation of the receptive fields, the mechanically insensitive fibers conducted at a slower velocity, had larger receptive fields defined by electrical stimulation, and responded more intensely to bradykinin and lactic acid, which are commonly released during episodes of myocardial

ischemia. These silent cardiac sensory afferent fibers appear to represent a novel population of cardiac sensory receptors that may function as nociceptors (60, 62, 223). Thus, the recruitment of the mechanically insensitive afferent fibers during myocardial ischemia likely contributes to the perception of angina pectoris.

### Cardiac vagal afferent fibers

Vagal afferents also innervate the heart. Action potentials transmitting nociceptive information from the heart to the brainstem are conveyed primarily in unmyelinated vagal afferent fibers. Sensory endings of these fibers are dispersed to all regions of the heart, but the density of the fibers varies from region to region (19,32,73,231,341,342). A greater concentration of vagal afferent fibers terminates in the inferior-posterior wall of the left ventricle (101, 357). As a result myocardial infarction in the inferior-posterior region produces bradycardia and hypotension (275, 362). In addition, occlusion of the left circumflex coronary artery more effectively evokes vagal reflexes than reflexes evoked during occlusion of the left anterior descending coronary artery (340). Thus, in summary, experimental evidence from animal studies suggests that activation of the vagal afferents most likely occurs when myocardial ischemia involves the inferior-posterior region of the left ventricle.

Most likely both chemosensitive and mechanosensitive receptors are activated during episodes of myocardial ischemia, similar to spinal afferents. Chemosensitive vagal afferents generally do not discharge with cardiac rhythm and do not respond to vascular distensions; on the other hand, mechanosensitive endings in control conditions commonly discharge one or two pulses with each cardiac cycle (19, 343). Impulses in chemosensitive vagal afferents significantly increase when bradykinin is applied to the surface of the heart or injected into the left atrium (175). Furthermore, prostaglandin E2 and reactive oxygen species as well as exogenous chemicals such as capsaicin, serotonin, nicotine, phenylbiguanide, and veratrum alkaloids also activate chemosensitive vagal fibers (7, 19, 315, 352). In contrast, mechanosensitive vagal afferents respond only to nicotine and veratrum alkaloids (240, 327). Myocardial ischemia resulting from occlusion of the coronary artery also increases neural activity in these vagal afferent fibers (341, 342). Most commonly changes in the ST segment of the ECG and bulging of the ventricle occur before vagal afferent activity increases. When vagal afferent activity begins to increase the activity displays cardiac rhythm but as the occlusion continues the discharge pattern becomes continuous. Thus, it appears that both mechanosensitive and chemosensitive vagal afferent fibers are excited during coronary artery occlusion.

Peripheral endings of large myelinated vagal afferents are located primarily in the atria and the venoatrial junction of the heart, with fewer originating in the ventricle and coronary arteries (73, 74, 87, 244, 344). Most commonly the systolic discharge of type A receptors is a function of the active tension developed by atrial muscle during contraction. During an atrial cycle, the discharge pattern of the receptors depends on both the degree of atrial distension and the state as well as extent of contraction. In contrast, B atrial vagal receptors depend intimately on static and dynamic changes in atrial wall tension (281, 282). Neither of these types of myelinated afferents appears to contribute to the nociceptive responses associated with angina.

To summarize this section, numerous chemicals are released during myocardial ischemia that can activate and/or sensitize spinal and vagal cardiac afferents, ultimately leading to the sensation of angina and pain referral to somatic structures. On the other hand, since there is an uneven distribution of vagal and sympathetic afferent fibers in different regions of the heart, if there is an imbalance in the excitation of these two groups of fibers then angina pectoris may or may not be experienced in a patient. The next section in this review will consider how the information from spinal and vagal afferents is processed in the central nervous system.

## Central Processing of Afferent Information

This section will discuss studies that have been conducted to explain the possible neurophysiological mechanisms that contribute to the characteristics of typical and, to a lesser extent, atypical angina pectoris. Generally, three main features characterize typical angina pectoris: (i) nociceptive information originating from the heart is commonly experienced as pain in somatic structures that innervate the same spinal segments that also receive afferent input from the heart (301); (ii) pain is referred to proximal and axial somatic structures but generally not to distal limbs (43); and (iii) pain is described as deep and aching, but not experienced as cutaneous superficial pain (191). As pointed out earlier, patients can experience atypical angina pain that is referred to the neck, jaw, or back. Data from neurophysiological studies help to explain most of these phenomena.

### Viscerosomatic convergence

We previously mentioned the convergence projection theory positing that visceral and somatic stimuli converge on a common population of central neurons, and this convergence can lead to both visceral pain and referred somatic pain. To begin to determine whether viscerosomatic convergence could explain anginal pain, initial studies concentrated on the spinothalamic tract (STT) and the spinoreticular tract (SRT) in the upper thoracic spinal cord, because these pathways were known to conduct somatic pain to the thalamus and reticular formation, respectively, and the upper thoracic cord receives sensory information from the heart. These studies, performed in cats and monkeys, demonstrated that electrical stimulation of cardiac spinal afferents excite about 80% of STT and SRT cells in the upper thoracic (T1-T5) segments.

Neurons were located in laminae I, V, VI, and VII of the spinal gray matter. The neurons also responded to bradykinin applied to the heart either epicardially or intracardially and to coronary artery occlusion. All of the neurons with cardiac input also received somatic input, primarily nociceptive input from muscles in the chest and upper limb. Collectively, these studies provided evidence supporting that the convergence projection theory is valid for STT and SRT neurons in the upper thoracic cord, and suggested that these neurons could both lead to sensations of angina and contribute to referral of pain to overlying somatic structures (16, 17, 34, 37-39, 109).

A consideration of the somatic responses of STT neurons is whether they are consistent with the sensations of angina. Generally, patients experience typical angina pectoris as a deep, diffuse, dull, and suffering type of pain, which contrasts with cutaneous pain that usually is described as sharp and well defined. The characteristics of angina pectoris are similar to those described for muscle pain in that it is deep, aching, and often associated with referred muscle hyperalgesia. Experiments performed on patients with angina symptoms have shown that the sensations between visceral pain and muscle pain are similar (176, 177). These patients compared their anginal pain with pain generated after hypertonic saline injections were made into muscle near the left interspinous ligament of C8-T1 spinal segments. They stated that the segmental localization as well as the onset, continuation, and character of the muscle pain were similar to the angina pectoris they experienced during ischemic episodes (176). Furthermore, as noted previously, typical angina pectoris radiates to proximal, axial areas including the chest, and occasionally it also radiates to the left proximal shoulder; on the other hand, pain is felt much less frequently in distal structures such as the arm and hand (27, 305, 334). These clinical observations led Hobbs et al. (147) to more closely examine the somatic field characteristics of STT neurons in the C3-T6 segments that received cardiopulmonary visceral input (Fig. 6). Although some STT neurons in all of these segments received cardiopulmonary input, the largest percentage of responsive neurons and the largest percentage of excitatory responses occurred in the T1-T6 segments. Weakest responses occurred in the cervical enlargement (C7-C8). Furthermore, STT neurons with proximal somatic fields (upper limb and chest) and that responded most intensively to pinch of muscle were more likely to receive cardiopulmonary input than neurons with distal somatic fields that primarily responded to cutaneous input. The latter neurons were located in the cervical enlargement. In summary, STT neurons in the upper thoracic spinal cord respond most intensively to cardiopulmonary input and receive predominantly somatic input from proximal muscle groups; these neurons likely contribute to referral of anginal pain to proximal muscles. STT neurons in the cervical enlargement receive weak cardiopulmonary input and respond best to cutaneous input from the distal arm and hand; the lack of cardiopulmonary input onto these neurons is likely a reason that anginal pain is not referred usually to distal structures. These conclusions are consistent with clinical observations that angina pectoris is referred most commonly to proximal axial somatic structures but not to the distal forearm and hand (139, 261, 305).

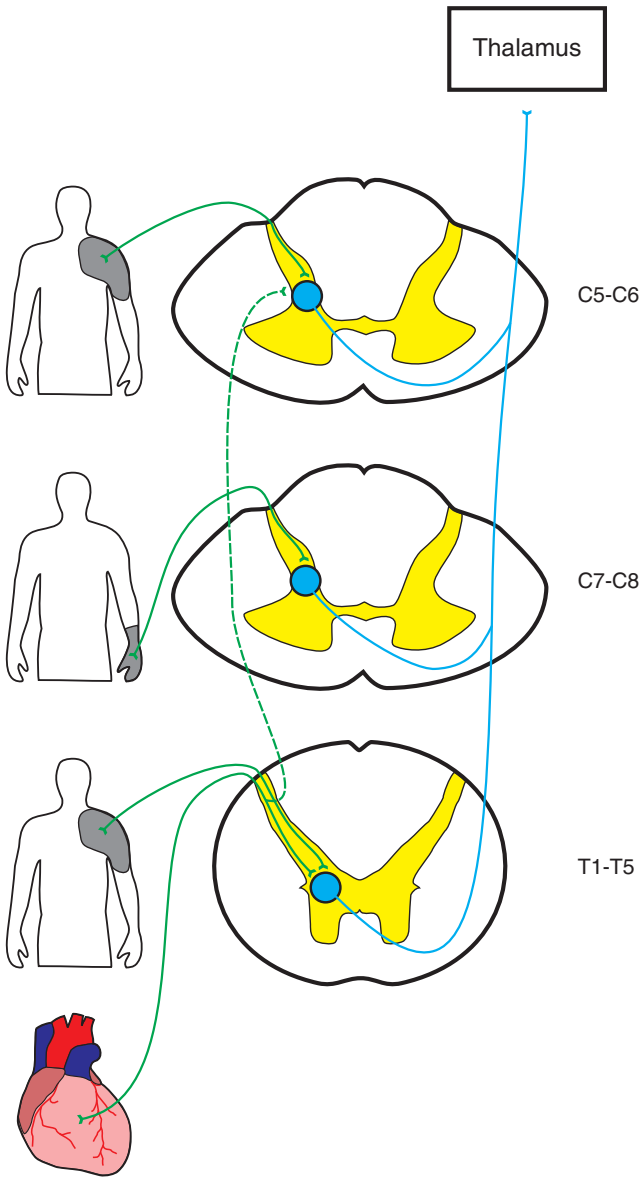



Figure 6 Patterns of convergence of cardiac and somatic inputs onto spinothalamic tract neurons in the upper thoracic and cervical spinal segments. The T1-T5 and C5-C6 segments receive converging nociceptive cardiac input and somatic input from the chest and upper arm, although the cellular responses to cardiac stimuli are more intense in T1-T5. Spinothalamic tract neurons in the C7-C8 segments receive no appreciable cardiac input and receive somatic input from the distal arm and hand. The dashed line indicates that the pathway(s) by which cardiac input reaches C5-C6 are not defined. All pathways in this diagram are excitatory.

Neuroanatomical reports have shown that cardiac visceral spinal afferent fibers do not travel in the DRG of the cervical spinal segments (154, 186, 353). Thus, signals resulting from activation of T1-T5 cardiac nociceptive afferent fibers may travel in a propriospinal pathway with terminals that

synapse onto cervical STT cells (239). Another possibility is that branches of the upper thoracic afferent fibers may traverse in the zone of Lissauer for several segments and then synapse on cervical STT neurons (329) (Fig. 6).

In summary, cardiac spinal afferent and somatic nociceptive afferent information converges onto a common pool of STT cells, which provides a substrate that may explain pain referral to overlying somatic structures. As a result of viscerosomatic convergence, typical angina pectoris most commonly produces a deep, diffuse, suffering pain that is generally referred to proximal and axial structures such as muscle, ligaments, and tendons.

## Role of neurotransmitters

We previously mentioned that myocardial ischemia stimulates spinal afferent sensory afferent fibers that respond to CAP and possess TRPV1 (152, 202, 267, 336). To determine if TRPV1 containing fibers transmitted this cardiac nociceptive information to neurons in the spinal cord, RTX was used to desensitize the fibers (173, 252, 336, 373). Recordings of extracellular potentials were made from individual T3 spinal neurons while cardiac nociceptive receptors were activated by injecting bradykinin or capsaicin into the pericardial sac. Both bradykinin and capsaicin excited approximately 80% of the responsive neurons in the superficial and deeper dorsal horn; the remainder of the cells responded to either capsaicin or bradykinin. After RTX was injected into the pericardial sac, excitatory responses of the spinal neurons to both bradykinin and capsaicin were abolished (267; Fig. 7). It is important to note that excitatory responses to noxious somatic stimuli converging onto these same neurons were not affected. Additionally, intrapericardial injections of capsazepine, a specific antagonist of TRPV1, sharply reduced the excitatory activity to capsaicin; however, the excitatory responses to bradykinin were not attenuated. These data support the idea that bradykinin-initiated responses of spinal neurons were associated with cardiac TRPV1-containing afferent fibers, but were not dependent on TRPV1 receptors. Thus, spinal neuronal responses to cardiac nociceptive stimuli, but not somatic stimuli, likely involve afferents containing TRPV1 receptors.

Although numerous studies have been conducted to describe the characteristics of the excitatory responses of specific spinal neurons and cells of origin of ascending pathways to nociceptive input from spinal cardiac afferent neurons, very little research has been done to identify specific neuromediator(s) that are released from the nociceptive cardiac afferent fibers at the spinal level during episodes of myocardial ischemia. Central terminals of spinal afferent fibers most likely release substance P and neurokinin A (NKA), glutamate (GLU), and calcitonin gene-related peptide (CGRP) (33, 81, 111, 123, 155, 163, 193, 251). Indirect evidence has shown that high concentrations of substance P are located in the spinal gray matter and are released at the spinal level during stimulation of visceral and somatic C-fiber afferent nerves (95,96,193,311,321,371,374). Direct evidence for the role of substance P being released in the spinal gray matter from cardiac spinal afferent fibers during myocardial ischemia comes from the results of a study by Hua et al. (163) (Fig. 8). The levels of substance P were determined by using antibody-coated microprobes that were inserted into the upper thoracic spinal cord in anesthetized rats. The microprobes detect differences in the release of immunoreactive substance P-like material during activation of cardiac spinal nociceptive

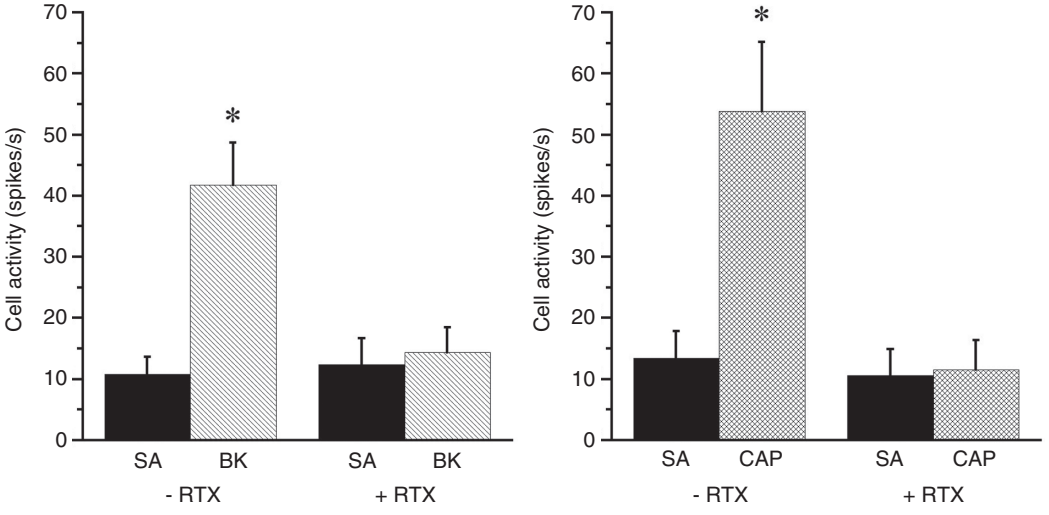



Figure 7 Effects of intrapericardial resiniferatoxin (RTX) on upper thoracic spinal neuronal responses to bradykinin (BK) and capsaicin (CAP). Intrapericardial BK or CAP was administered approximately 20 to 30 min after pretreatment with RTX. The results show that increased activity responses to BK or CAP were markedly reduced after RTX treatment. Data are presented as mean ± SEM. $^*P < 0.05$ compared with spontaneous activity (SA) before (−RTX) and after (+RTX) administration of RTX. (Reprinted, with permission, from 267.)

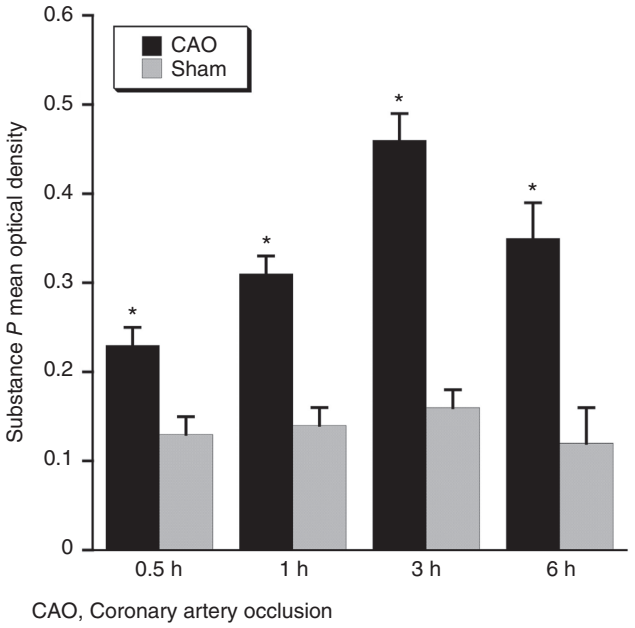



Figure 8 Effects of coronary artery occlusion on spinal levels of substance P. Filled bars represent the mean optical density of antisubstance P immunoreactive material in the spinal cord of rats receiving coronary artery occlusion (CAO) for 0.5, 1, 3, or 6 h. Hatched bars represent the mean optical density of antisubstance P immunoreactive material in spinal cord of rats at 0.5, 1, 3, and 6 h following sham surgery. Results indicate that the levels of substance P in the spinal cord were significantly elevated following CAO. Data are presented as mean ± SEM. $^*P < 0.05$ compared with time-matched sham surgery group. (Reprinted, with permission, from 132.)

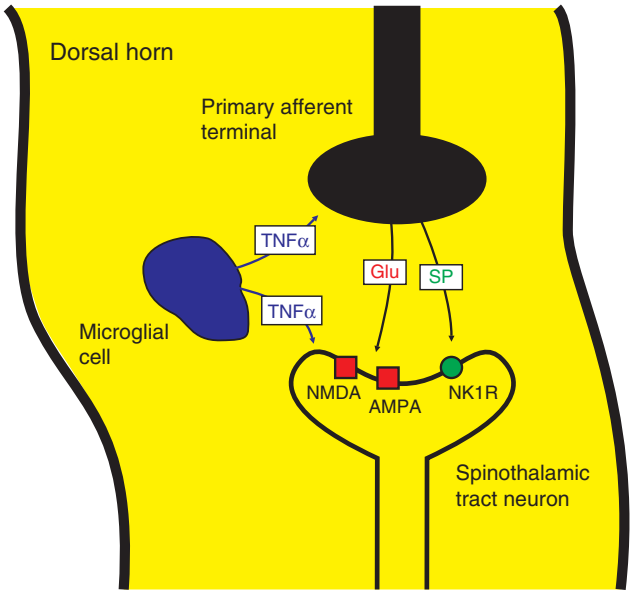
afferent neurons by transiently occluding the left anterior descending coronary artery. As a result of these transient and focal ischemic episodes, an increased release of substance P was detected in the superficial dorsal laminae I and II and deeper laminae including laminae III-VII. This increased release correlated with the activation of the spinal cardiac nociceptive afferent fibers, because this increased expression of substance P was sustained during the period of time when the coronary artery was occluded. However, bilateral transections of the T2-T5 dorsal roots eliminated the increased release of substance P during the coronary artery occlusion. The role of substance P being released during myocardial ischemia gained further support when the use of molecular and morphological profiles showed that substance P and preprotachkinin mRNA were upregulated in the T1-T5 dorsal horn during occlusion of the coronary artery (132). A more recent study showed that the release of substance P in the upper thoracic spinal gray matter requires, in part, the involvement of TRPV1 receptors (328). This is based on the observations that injections of capsazepine, a TRPV1 receptor antagonist, into the gray matter of the T4 segment reduced the release of substance P during occlusion of the coronary artery. These data suggest that the substance P released in spinal cord dorsal horn sites is a principal neuropeptide mediator associated with transmission of nociceptive information during myocardial ischemia, and is released partially via a TRPV1 mechanism (328).

Although substance P is released in the spinal gray matter during episodes of myocardial ischemia, injections of a mixture of algogenic substances (bradykinin, 5-hydroxytryptamine, adenosine, and PGE2) did not alter the pattern of substance P release in these same areas of gray matter within the T4 spinal segment (163). However, the previous discussion emphasized that the discharge rate of spinal neurons, SRT cells, and STT cells is significantly increased during intrapericardial injections of bradykinin, algogenic chemicals, coronary artery occlusion (17, 34, 38, 39, 66, 265). An important observation that may partially explain the differences observed between the occlusion studies and the algesic chemical studies is that a subpopulation of neurons responded differentially if the left descending coronary artery or the left circumflex artery was occluded. Diffuse activation of epicardial spinal afferent fibers with chemicals compared with regional activation of afferents resulting from coronary artery occlusion possibly may produce differential and discrete release of neuromediators from the cardiac nociceptive spinal afferents that project into the spinal gray matter (163). Alternatively, an alteration of substance P release may not have been detectable with the technique used.

## Central sensitization

Central sensitization is an expression of plasticity of neurons within the spinal gray matter. Continual barrages of impulses being transmitted from the site of injury or inflammation via nociceptive afferent fibers can evoke patterns of activation, modulation, and modification that can enhance the responsiveness of spinal neurons and neurons that transmit nociceptive information to supraspinal levels with resultant pain sensation (370). Central sensitization results from changes in the synaptic connections between the nociceptive primary afferent fibers and cells in the spinal gray matter. Noted above, these central terminals release numerous transmitters including glutamate, substance P, and CGRP, along with synaptic neuromodulators such as brain-derived neurotrophic factors. These transmitters and neuromodulators activate particularly *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors which are activated by the synaptic release of glutamate. Substance P, which is coreleased with glutamate by C-fiber peptidergic nociceptors, activates NK1 receptors on neurons and is also involved in the generation of central sensitization (see Ref. 188 for review). Most of the information that contributed to our understanding of central sensitization resulted from studies that utilized somatic afferent nociceptive input. Therefore, minimal information exists about the role of visceral nociceptive afferent input in generating central sensitization, specifically cardiac nociceptive input. Studies conducted on other visceral organs lead to the suggestion that increased nociceptive input can contribute to central sensitization. In a human study, repeated noxious distensions of a

balloon placed in the colorectal region increased sensitivity to pain and expanded the area of referred pain to overlying somatic structures (236). Experiments conducted on animals demonstrated that myocardial ischemia resulting from coronary artery occlusions release substance P in the areas of spinal gray matter that contain cells of origin of the STT and other ascending pathways that transmit nociceptive information to supraspinal nuclei that participate in pain sensation (132, 328). However, even though substance P is released there is no evidence that these spinal neurons are sensitized. On the other hand, spinal neurons possessing the substance P receptor are necessary for development of central sensitization resulting from injections of capsaicin into hind paw (180). Furthermore, lamina I neurons expressing the substance P receptor increased in number and rostrocaudal extent after visceral inflammation of the colon (153). Thus, the release of substance P from cardiac nociceptive afferent input likely contributes to central sensitization of STT neurons and other spinal neurons resulting from ischemic heart disease, although direct evidence for this suggestion is lacking.

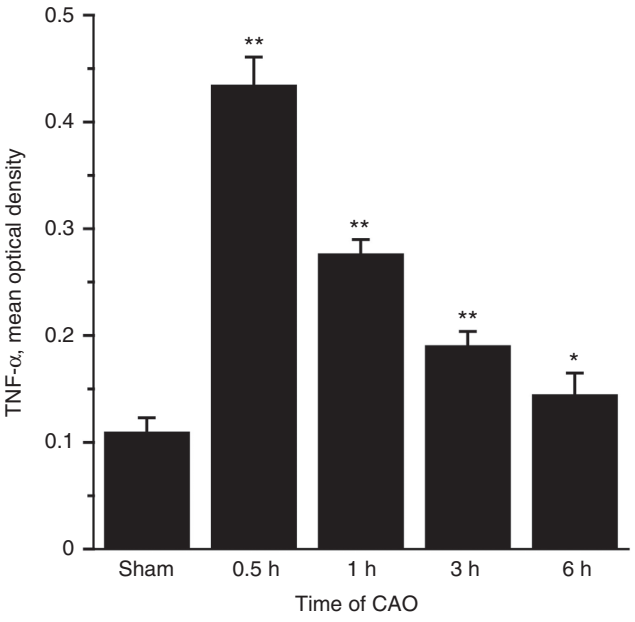



AMPA, α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptor; Glu, glutamate; NK1R, neurokinin 1 receptor; NMDA, N-methyl-D-aspartate receptor; SP, substance P; TNFα, tumor necrosis factor alpha

Figure 9 Neurotransmitter interactions within the spinal dorsal horn. Nociceptive spinal cardiac afferents release both glutamate and substance P onto spinothalamic tract neurons. Glutamate stimulates NMDA and AMPA receptors, and substance P stimulates NK1R receptors. Under appropriate conditions microglial cells can release TNF-α which can influence both the presynaptic and postsynaptic nerve terminals.

## Glia and neural plasticity

In addition to central sensitization of nociceptive ascending pathways via activation of nociceptive afferent fibers, research is accumulating to also support an important role that glia in the spinal cord serve as dynamic modulators of neural plasticity in central neuronal networks. Experimental animal models of peripheral inflammation, nerve injury or spinal injury have been used to show how glia contribute to central sensitization and pathological pain (44, 83, 212, 361) (Fig. 9). As discussed previously, under normal circumstances glutamate is the major excitatory transmitter that is released from the presynaptic terminals of nociceptive primary afferent fibers, and binds to NMDA, AMPA, and metabotropic glutamate receptors on the postsynaptic spinal neurons (26, 210). The opening of these channels results in an influx of cations that lead to generation of action potentials in the spinal neurons including the STT. Normally, the glutamate transporters, glutamate transporter 1 and glutamate-aspartate transporter, located in astrocytes, clear synaptic glutamate to control the levels of glutamate in the synaptic clefts (31, 122, 189, 287, 299). However, these transporters become dysregulated after they are exposed for long periods to high levels of synaptic glutamate. As a result glutamate uptake is decreased and the accumulation of excessive glutamate contributes to central sensitization of spinal neurons. In addition to glutamate, substance P and ATP can also excite microglia and astrocytes (227). The barrage of afferent input that continues to release glutamate, substance P and other neurotransmitters sustains the excitation of glia. This excitation induces the activation of extracellular signal-regulated kinases (ERK), p38, and c-Jun N-terminal kinases (JNK) that then activates transcription factor nuclear factor-kB (NF-kB). Activation of NF-kB induces the synthesis of inflammatory factors such as TNFα, IL-1B, IL-6, nitric oxide (NO), and PGE2 (see Ref. 227 for review). Most of the information that generated these key findings regarding the glia and cytokines resulted from activation of somatic afferent fibers in experimental animal chronic pain studies. A few studies have addressed how excitation of visceral spinal afferent fibers contributes to the production of inflammatory cytokines, specifically TNFα and to a less extent IL-1B. Further support for the ability of visceral afferents to activate spinal microglia has been demonstrated by using colorectal distension and neonatal colonic irritation. Injection of the microglia activator, fractalkine, into the spinal cord of normal rats induced visceral hyperalgesia during noxious colorectal distension (302). In addition, acute treatment with minocycline, an inhibitor of microglia, prevented visceral hypersensitivity to colorectal distension. Neonatal irritation of the colon, which produces peripheral and central sensitization in adult animals, caused an increased proliferation of microglia in the spinal gray matter (8). All these studies demonstrate that cytokines released from microglia can generate central sensitization of spinal neurons. Related to cardiac pain, TNFα is also one of the inflammatory factors released from glia that has been associated with myocardial ischemia. Niu et al. (238) showed that TNFα was upregulated in neurons of the dorsal horn 30 min after the onset of ligation of the left anterior descending coronary artery of a rat model, and the upregulation was sustained even six hours after the onset of the occlusion (Fig. 10). Francis et al.




CAO, Coronary artery occlusion
TNF-α, Tumor necrosis factor-alpha

Figure 10 Effects of coronary artery occlusion (CAO) on TNF-α in rat spinal cord. Bars represent mean optical density of immunoreactive material for TNF-α in the spinal cord of rats receiving coronary artery occlusion for 0.5, 1, 3, and 6 h or sham surgery. Results indicate that TNF-α is expressed in the spinal cord in response to CAO. Data are presented as mean ± SEM. $^{**}P < 0.01$ versus sham, $^{*}P < 0.05$ versus sham. (Adapted, with permission, from 238.)

(112) demonstrated that, after the left coronary artery of a rat model was ligated for two hours, TNFα and IL-1B were significantly increased in the heart, plasma, and the hypothalamus. The cardiac spinal afferents were responsible for generating the increase in cytokines in the hypothalamus, but the vagus nerve was necessary to fully express these cytokines in the heart and plasma (112). Activation of cytokines in the brain may be related to excitation of nociceptive cardiac sensory afferent fibers, because it has been shown that neuropathic pain resulting from chronic constriction of somatic nerve is associated with alteration in ambient levels of TNFα and IL-B in the brain and hypothalamus (75, 156). This does not limit the role of other inflammatory factors, but additional studies need to be done to fully understand how the effects of microglia and astrocytes, along with their transporters, and inflammatory factors contribute to cardiac pain.

## Vagal suppression and central processing

The previous discussion emphasized that nociceptive cardiac stimuli activate spinal afferents that excite STT and SRT neurons transmiting this information to the brainstem and thalamus. These neurons also respond to noxious somatic input which helps account for pain referral to the proximal portion of the upper limb and chest. Results of this work do not, however, easily explain atypical anginal pain referral to the jaw and neck, nor possible mechanisms to account for silent cardiac ischemia. This led to studies that examined possible neural components for modifying nociceptive cardiac input to the central nervous system. The first of these to be examined were pathways related to activation of the vagus nerve, based on two primary observations. First, myocardial ischemia activates unmyelinated vagal afferents, and these afferents can inhibit sympathetic vasomotor outflow and suppress sympathetic efferent activity (178, 197, 317, 339, 342, 344). This leads to the possibility that vagal activation might modulate central nociceptive pathways that contribute to cardiac pain. Second, results from conscious animal models demonstrated that activation of vagal afferent pathways can decrease pain sensitivity (278). For example, pain sensitivity is reduced in hypertensive rats, but the sensitivity increases after vagotomy (379). In addition, right cervical vagotomies reverse opioid-mediated analgesia and reduce stress-induced analgesia in spontaneously hypertensive rats (203,204). Also, it is possible that these pathways may contribute to increases in pain sensory and pain thresholds to tooth pulp stimulation in humans with borderline or essential hypertension (125, 292, 380).

In addition to the findings mentioned above, the vagus nerves may mediate the referral of atypical anginal pain to the neck and jaw. Human sympathectomy studies, dental case reports, and osteopathic literature provided the background to examine an explanation for pain referral to the neck and jaw region during myocardial ischemic episodes in an animal model. Early clinical observations showed that neck pain was expressed after, but not before, sympathectomy (to interrupt spinal visceral afferents from the heart) was performed to reduce pain in patients suffering from refractory angina pectoris (194, 367, 368). These investigators proposed that the vagus nerve was the most likely pathway for transmitting information to the upper cervical region. Articles published in the dental literature also report that myocardial ischemia elicits craniofacial pain as the only complaint in a very small population of the dental patients (184, 185, 346). A recent case report also raised the possibility that vagal afferents may mediate angina pectoris expressed as jaw and tooth pain (233).

Activation of vagal afferents suppresses the spontaneous and evoked activities of STT and spinal neurons with unidentified projections located in widespread segments of the spinal cord extending from the lower cervical to lumbosacral segments (10, 63, 148, 285, 288). In the upper thoracic cord, vagal stimulation inhibited the spontaneous activity of 70% of STT cells that responded to cardiac nociceptive input (10) (Fig. 11). To confirm that the effects of vagal stimulation originated from the cardiopulmonary region, electrical stimulation of the cardiac branch of the vagus produced effects similar to stimulation of the left thoracic vagus but no inhibition was elicited when vagal stimulation was applied between the heart and diaphragm (10, 148). In addition, the evoked STT cell activity resulting from intracardiac injections of bradykinin was sharply reduced during stimulation of the left thoracic vagus nerve; the vagal effects were eliminated after the cervical vagi were transected (11). Somatic responses also were inhibited

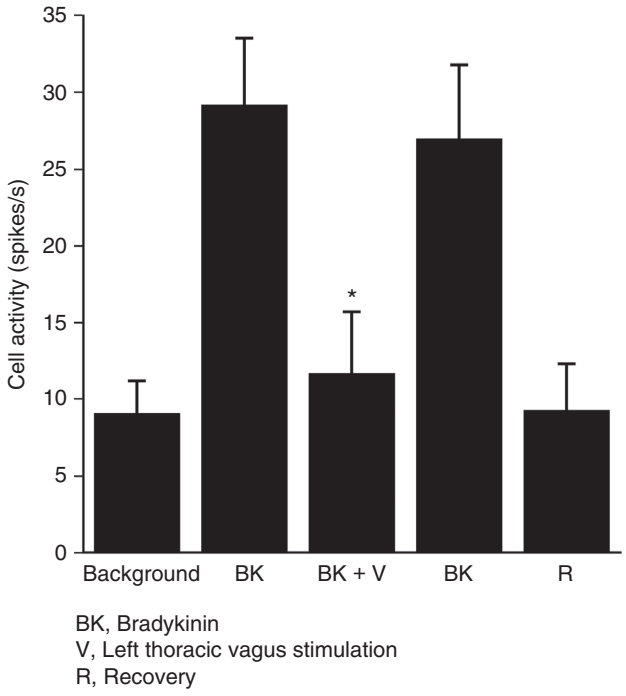



Figure 11 Cell responses to intracardiac injection of bradykinin (BK) and effects of left thoracic vagus nerve simulation on those responses in monkeys. Background cell activity of spinothalamic tract neurons was recorded and then BK was injected into the left atrium. At the peak of the response to BK, the left thoracic vagus nerve was stimulated for 5 s and cell activity was recorded (BK + V). Cessation of stimulation the left thoracic vagus nerve caused the cell activity to return to the bradykinin-stimulated level (second BK). Thus, left vagus nerve stimulation reduced neuronal responses to intracardiac BK. Data are presented as mean ± SEM. *$P < 0.001$ compared to BK. (Adapted, with, permission from 11.)

by vagal stimulation. Thus, activation of vagal afferents suppresses both cardiac and somatic input to upper thoracic STT neurons.

Hua et al. (162) provided evidence regarding the neurotransmitters and neuromodulators that may be involved in vagal suppression of thoracic neuronal activity. They used antibody-coated microelectrodes to measure the release of substance P and dynorphin in the upper thoracic spinal gray matter. The measurements were made during left coronary artery occlusions alone and during electrical stimulation of the proximal end of the left thoracic vagus. The results showed that during coronary artery occlusion vagal stimulation increased the release of dynorphin and reduced the release of substance P in laminae I-VII of the thoracic spinal gray matter. Thus, release of dynorphin may account for some or all of the suppression of substance P during a myocardial ischemic episode (163). This is the first evidence that the interaction between these two peptides may explain how nociceptive cardiac afferent information is attenuated by vagal stimulation during coronary artery occlusion. Thus, vagal afferent fibers primarily from the heart are responsible for suppressing nociceptive somatic and cardiac input to upper thoracic STT cells during activation of the nociceptive cardiac spinal afferent fibers. These results suggest mechanisms for decreasing pain sensitivity and increasing pain threshold.

## Vagal afferents and C1-C2 processing

What are the specific pathways by which the vagus nerves can affect the activity of spinal neurons? Nociceptive information transmitted via vagal afferents terminates primarily in the nucleus tractus solitarius (NTS) of the medulla, primarily ipsilaterally but also contralaterally (25). Physiological experiments have shown that the NTS is critical for vagal suppression of activity in spinal neurons (286). The NTS may serve as relay to activate other regions that suppress spinal neuronal activity.

One possibility is a relay from the NTS to the upper cervical spinal cord. The upper cervical cord receives dermatomal input from the neck; if neurons receiving this input also received cardiac input, then this could help explain anginal pain referral to the neck. A study in the osteopathic literature by manual medicine physicians showed that a small population of patients with cardiovascular disease had changes in tone of paraspinal muscles in the C1-C3 segments, although the most common segmental distribution of increased paraspinal tone was from segments T1-T5 (21). Upper cervical (C1-C2) segments have propriospinal neurons modulating nociceptive spinal processing. Anatomical studies in monkeys (49), cats (209, 376), and rats (225) have shown that cell bodies of these propriospinal neurons are located in the lateral cervical nucleus, dorsal horn, lamina X, and ventral horn of the upper cervical spinal segments. An argument will be developed to suggest that propriospinal cells are activated by vagal nerve stimulation to suppress nociceptive spinal input in segments below the C1-C2 segments.

C1-C2 propriospinal neurons modulate nociceptive afferent input to upper thoracic neurons (271). Glutamate pledgets were placed on the dorsal surface of the C1-C2 segments of the spinal cord to activate cell bodies but not axons passing through these segments. Glutamate activation of C1-C2 neurons decreased background activity and/or excitatory responses of more than 75% of upper thoracic spinal neurons to intrapericardial injections of bradykinin (Fig. 12). Furthermore, after spinal transection at rostral C1 in five animals, glutamate at C1-C2 still significantly reduced excitatory responses of five neurons to cardiac application of bradykinin, indicating that brainstem mechanisms were not required for the inhibitory responses. Thus, intraspinal activation of C1-C2 propriospinal neurons primarily produces descending inhibition of excitatory responses of thoracic spinal neurons to noxious visceral stimuli. These observations led to studies that were designed to explore neural mechanisms of referred pain in the upper cervical spinal cord. To initiate this exploration, recordings of extracellular potentials were made from STT cells located in the C1-C2 spinal segments (64, 66). Electrical stimulation of cardiopulmonary visceral spinal afferent fibers and thoracic vagal afferents, coronary occlusion, and injections of algesic chemicals into the heart before and after

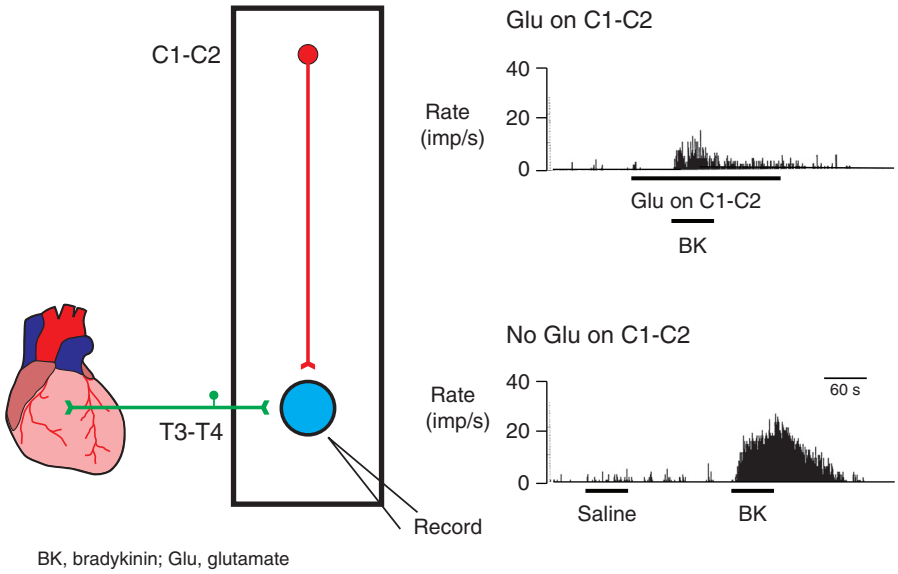



Figure 12 Modulation of thoracic neuronal responses by the C1-C2 segments. Neuronal activity was recorded from neurons with unidentified projections in the T3-T4 segments in rats. The panels show the rate of discharge of extracellular potentials from the spinal neurons. The lower panel on the right shows that the neuron responded robustly to bradykinin (10-5 M, 0.2 mL) injected into the pericardial sac via a catheter. In the upper panel on the right, a glutamate 2.2 mm pledget (1.0 M absorbed onto filter paper) was placed on the surface of the spinal cord at the C1-C2 segments before application of bradykinin to the heart. The response to bradykinin was substantially reduced in the presence of glutamate, suggesting that a propriospinal pathway from the upper cervical cord to the upper thoracic cord suppresses neuronal responses. The neurotransmitter(s) mediating inhibition is/are not yet known. In this and subsequent figures, pathways colored red are inhibitory.

bilateral vagotomy were used to determine the mechanisms and pathways that activate C1-C2 STT cells.

Anatomical studies indicate that vagal afferent fibers may project directly or indirectly to the C1-C2 propriospinal neurons. Only 6% of vagal afferent fibers project directly to the C1-C2 spinal neurons (214). Therefore, most vagal afferents likely terminate in the NTS and synapse on cells with axons projecting to the C1-C2 segments. Supporting this concept, retrograde transport experiments show that solitariospinal neurons project to the midcervical and upper thoracic spinal segments (230). By extrapolation it is possible that C1-C2 propriospinal neurons also receive input from the NTS.

Experimental studies suggest that the processing of cardiac nociceptive information via the vagus involves a spinal network in the C1-C2 segments. Electrical stimulation of vagal and cardiac sympathetic nerves showed that STT and non-STT spinal neurons in C1-C2 were more strongly excited by stimulation of vagal afferents than of spinal cardiac afferent fibers, but nevertheless both afferent pathways activated the cells (64, 262). Note that the excitatory responses from vagal stimulation are opposite the inhibitory responses produced at lower levels of the spinal cord. To excite upper cervical neurons, spinal cardiac afferent input likely enters the spinal cord at upper thoracic segments and synapses on cells with axons that travel in the ventrolateral quadrant to synapse on the C1-C3 spinal neurons (381). The somatic receptive fields for these cells are located most commonly in the jaw, neck, ear, and upper arm. Somatic fields from the ipsilateral neck and/or shoulder regions enter the spinal cord via the upper cervical DRG (141). The variable locations of the somatic receptive fields may result from overlapping termination of primary afferent fibers originating from different segments of the spinal cord. Referral in the more caudal somatic fields may result from projections that originate at the C5-C7 segments (326, 363).

Injections of algesic chemicals into the pericardial sac excited STT and non-STT spinal neurons in upper cervical segments. Since both vagal and spinal cardiac afferents excite upper cervical neurons, the evoked activity could have been mediated by either or both sets of afferents. Vagotomy markedly reduced the evoked activity from cardiac application of algesic chemicals, suggesting that the excitatory responses were primarily vagally mediated (66, 262).

Recording from antidromically activated propriospinal neurons is the final piece of evidence for the role the C1-C2 propriospinal pathway plays when vagal afferents are stimulated to modulate nociceptive responses of spinal neurons. Electrophysiological studies in monkeys and rats were used to determine if descending axons of C1-C2 neurons respond to vagal sensory inputs. The axons of the studied neurons projected to the thoracic or lumbar spinal segments (65, 382). Electrical stimulation of the vagus increased the activity of approximately 50% of these propriospinal neurons. To suggest that vagal afferent fibers originated from the cardiopulmonary region, stimulation of the abdominal vagus did not excite neurons that were activated by thoracic

vagal stimulation. Thus, these results suggest that modulation of spinal nociceptive processing by vagal stimulation may involve synaptic connections with propriospinal neurons of the upper cervical segments.

Summarizing the vagal and C1-C2 studies, noxious stimuli in the heart activate vagal afferents that primarily terminate in the NTS. The NTS projects either directly or indirectly to the upper cervical spinal cord, accounting for vagal excitation of STT and propriospinal neurons. The viscerosomatic convergence onto these STT neurons likely accounts for atypical anginal pain referral to the neck and jaw. Activation of the propriospinal neurons helps explain how vagal stimulation suppresses evoked responses of viscerosomatic inputs to upper thoracic STT neurons (Fig. 13).

## "Atypical" angina and women

As discussed in the introduction, men most commonly experience typical anginal pain which is referred to the chest and upper arm, but women commonly experience atypical angina that is referred to the jaw, neck, shoulders, and back (85,88,256). The quality of the pain also is different. A single animal study examined possible sex differences in responses of upper thoracic neurons to cardiac input (195). Recordings of extracellular action potentials were made from T3 spinal neurons that responded to noxious chemical stimulation of cardiac afferent fibers and mechanical somatic stimulation in anesthetized male and proestrus female rats. Results of this study revealed that responses of the spinal neurons to cardiosomatic stimulation were not significantly different between males and females even though the estradiol levels were different. The locations of the somatic fields in the upper thoracic chest region were also similar. One limitation of this study was that the experiments were conducted in normal experimental animals, rather than animals with a chronic condition. A related investigation found that responses of postsynaptic dorsal column neurons to colonic distension were significantly higher in proestrus female rats than in the males (359). Perhaps upper thoracic neuronal responses would be different between male and proestrus female rats with a chronic cardiovascular condition (221). An additional consideration might be to repeat the study by recording from spinal neurons in the C1-C2 segments that respond to mechanical somatic stimulation of the neck and jaw, and receive convergent input from cardiac nociceptive stimulation (262). This consideration is suggested because women more commonly experience referred anginal pain in the neck than men. Thus, currently there are no known neurophysiological mechanisms that explain the differences in expression of typical versus atypical anginal pain.

## Role of the postsynaptic-dorsal column pathway

The emphasis of the previous discussion for spinal ascending pathways that mediate cardiac nociception are the STT and to a lesser extent the SRT. There are other ascending

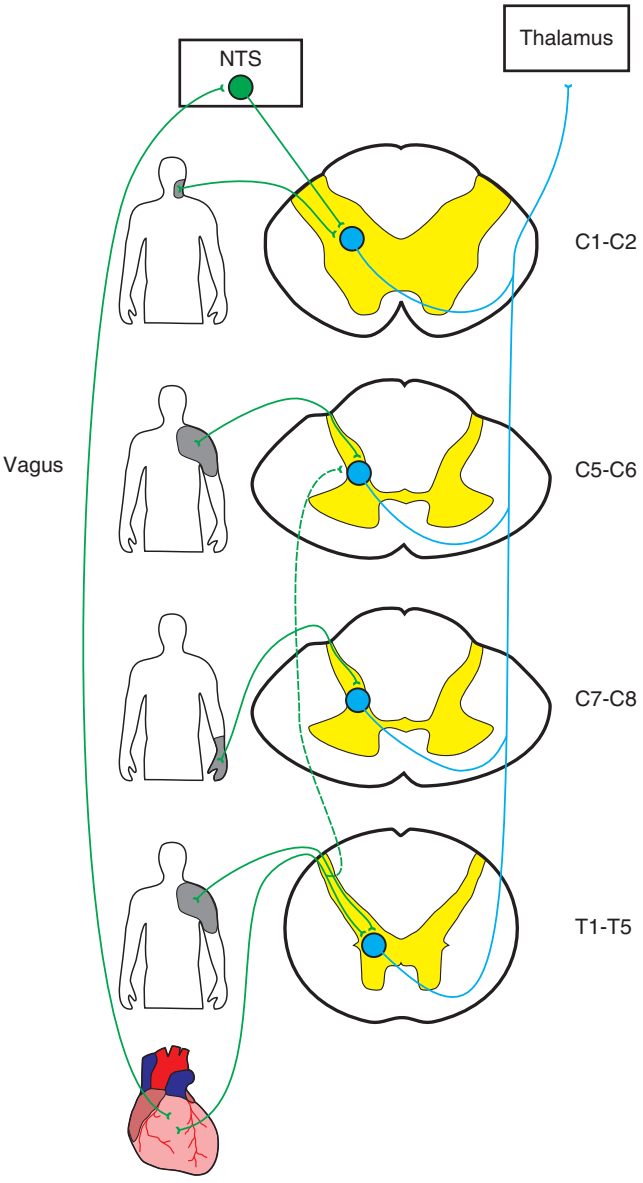



Figure 13 Convergence patterns of spinal, vagal, and somatic afferents onto spinothalamic tract neurons in different spinal segments. The vagal pattern is superimposed on Figure 6. Vagal afferents transmitting cardiac nociceptive information terminate in the nucleus of the solitary tract, which then excites neurons in the C1-C2 segments. These spinothalamic tract neurons receive somatic input from the neck region, but do not receive significant input from spinal cardiac afferents. All pathways in this diagram are excitatory.

pathways that could contribute to cardiac nociception. Among these pathways are the spinosolitary (219), spinoparabrachial (40, 57, 213, 220, 253) spinomesencephalic (375, 377), and spinohypothalamic tracts (48). No work to date has examined possible cardiac input to these pathways.

On the other hand, one additional ascending pathway, the postsynaptic-dorsal column pathway (PSDC), does transmit nociceptive visceral information. Clinical studies indicate that midline lesions of only the dorsal column at the

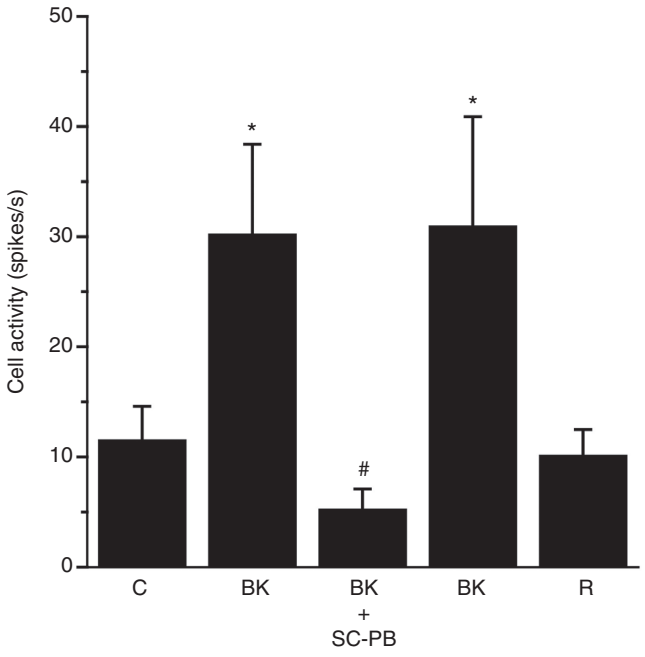
T10 spinal level relieve pelvic cancer pain in terminally ill patients (23, 146, 234). Subsequent neurophysiological and behavioral studies supported the clinical findings that PSDC neurons transmit visceral nociceptive information. Electrical stimulation of the gracile nucleus antidromically activated lumbosacral neurons that responded to noxious colorectal distension in rats (6-8,146) and primates (7). Noxious stimulation of the uterus, vagina, cervix (32), and pancreas (358) excite the PSDC in rats. In behavioral studies in rats, dorsal column lesions resulted in significantly reduced writhing-like behavior that resulted from duodenal pain (102), restored normal rearing behaviors in rats with pancreatitis (158), and restored normal exploratory activity in rats with severe colonic inflammation (246). Based on this information, we hypothesized that nociceptive visceral information from the heart would also be transmitted in the PSDC (129). Electrical stimulation of the cuneate nucleus and of the ventrolateral funiculus were used to antidromically activate PSDC neurons and STT neurons in the T3-T4 spinal segments of anesthetized rats, respectfully. Neuronal responses of these two populations were used to compare the effects of intrapericardial injections of saline (1.0 mL saline) that provided mechanical stimulation and of intrapericardial injections of algogenic chemicals (bradykinin, serotonin, adenosine, histamine, and prostaglandin E2) to determine the nociceptive responses. Of the PSDC neurons, 43% responded to mechanical stimulation, but only one responded to noxious chemical stimuli. In contrast, all of the STT cells responded to noxious chemical stimulation and 58% responded to mechanical stimulation. In short, mechanical but not nociceptive chemical stimulation activated PSDC neurons in the gray matter of the upper thoracic segments (129). The differences in processing nociceptive information between the upper thoracic and lumbosacral segments are most likely dependent on the preferred modality of pain between the heart and all of the abdominal and pelvic viscera. Episodes of myocardial ischemia cause the release of chemicals that activate chemosensitive cardiac afferents resulting in angina pectoris (76), whereas noxious distension of hollow organs excite mechanoreceptors that transmit noxious abdominal and pelvic information (50).

## Neural processing in the brainstem

Two regions in the brainstem have been examined for their potential effects on modulating cardiac nociceptive input: nucleus raphe magnus (NRM) in the medulla and the subcoeruleus/parabrachial region (SC-PB) in the pons. Perhaps the best known role of NRM is its modulation of pain, although the raphe nuclei participate in numerous homeostatic realms (see Ref. 208 for review). Activation of NRM generally inhibits spinal nociceptive transmission from somatic structures (22,105,124). These observations led to an examination of the effects of stimulating NRM on responses of upper thoracic STT neurons to cardiac stimulation (14). NRM stimulation inhibited the responses of these neurons to intracardiac bradykinin as well as to noxious and innocuous somatic stimulation. Raphe spinal neurons themselves receive noxious and innocuous input from the heart that can be mediated by either spinal or vagal afferents. These cells also receive input from other sensory modalities (35, 36). The responses of these neurons were complex, however, because the effects of vagal stimulation appeared to depend on the background rate of discharge: at spontaneous rates of activity vagal stimulation was excitatory, and at activity evoked by a stimulus vagal stimulation generally produced inhibition. Additional evidence that NRM receives vagal input comes from observations that inactivating NRM with either lidocaine or ibotenic acid, a selective neurotoxin for disruption of cell bodies, attenuates vagal inhibition of lumbosacral somatic responses (276, 277, 287).

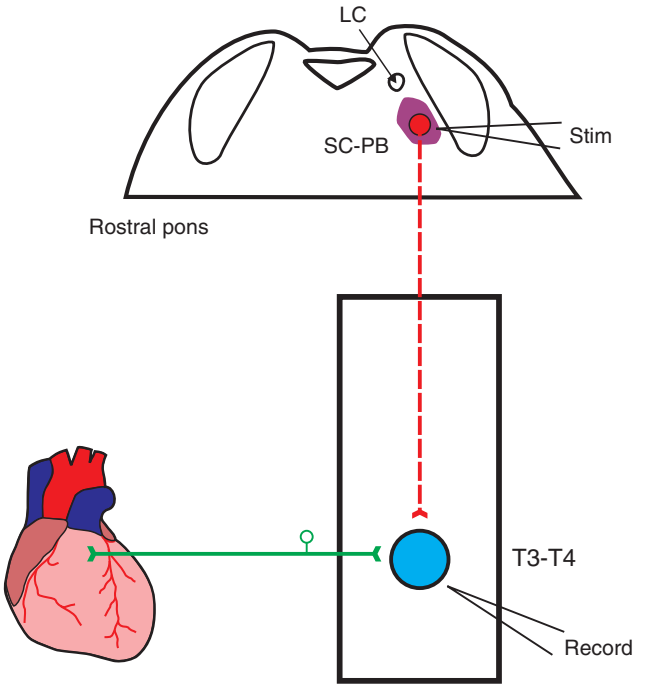
Pharmacological and behavioral studies have shown that the SC-PB is important for modulating nociceptive afferent input onto spinal neuronal networks processing this information. Injections of the muscarinic antagonist carbachol into the parabrachial region markedly suppressed nociceptive responses to tail flick latency test, calibrated pinch test, and subcutaneous formalin test (174). Also, lesions of the ventral parabrachial region appeared to attenuate morphine analgesia (136). Furthermore a significant group of cells in this region have axons that project to the gray matter of the spinal cord (138,337,364,365]. Finally, the caudal NTS has several axons that terminate in the medial and lateral parabrachial nuclei (24) which leads to the possibility that cardiac vagal information could relay to SC-PB. This information set the stage to determine if activation of neurons in the SC-PB region suppressed the responses of STT cells to nociceptive cardiac input. Electrical stimulation of ipsilateral or contralateral sites in the SC-PB region markedly suppresses the increased upper thoracic cell activity after injecting the algesic chemical, bradykinin, into the heart (45) (Fig. 14). Furthermore, activation of the SC-PB also reduced STT cell responses to noxious mechanical stimulation of their somatic receptive fields that converged on the neurons receiving cardiac nociceptive input (127). The limitation of this study is that it did not directly demonstrate that stimulation of vagal nociceptive input activates this region of the brainstem. However, a study in rats showed that relays in the locus coeruleus/subcoeruleus play an important role for vagal afferent produced suppression of spinal nociceptive transmission of noxious somatic stimuli (287). Bilateral injections of ibotenic acid into the locus coeuleus/subcoeruleus region markedly suppressed nociceptive spinal activity during vagal afferent stimulation. Combining the studies of electrical stimulation of the SC-PB with disruption of cell bodies in this region strongly suggest that activation of neurons in the SC-PB region modulates cardiac nociceptive input that may lead to cardiac pain (Fig. 15).

It is certainly possible that additional brainstem regions participate in the modulation of cardiac input to the central nervous system. The complex patterns of anginal referred pain possibly argue that wider regions of the brainstem are likely involved in these responses.




C, Control
BK, Bradykinin
SC-PB, Subcoeruleus-parabrachial stimulation
R, Recovery

Figure 14 Effects of subcoeruleus-parabrachial stimulation on spinothalamic tract cell responses to bradykinin in monkeys. The increase in cell activity caused by bradykinin was significantly greater than control (*$P < 0.05$). Subcoeruleus-parabrachial stimulation reduced cell activity below the bradykinin level (#$P < 0.05$). (Reprinted, with permission, from 45.)




LC, locus coeruleus; SC-PB, subcoeruleus-parabrachial region; Stim, stimulate

Figure 15 Modulation of thoracic neuronal responses by the subcoeruleus and parabrachial regions of the pons. Stimulation of this region inhibits neuronal responses to noxious spinal cardiac input. The dashed line indicates that the specific pathway(s) mediating this effect are not defined.

## Thalamo-cortical neural processing

Much of the work summarized previously emphasized the STT. Thus, electrophysiological (16, 37, 157), algesic chemical (17, 38), Fos (3, 84), and positron emission tomography (295, 296) studies have demonstrated that nociceptive cardiac and somatic information ascends to the lateral and medial thalamus. The lateral thalamus is composed primarily of the ventroposterolateral and ventroposteromedial nuclei containing cells with axons relaying information to the primary somatosensory cortex. This region is important for processing both somatic and visceral input that contributes to spatial location, intensity, and duration of the nociceptive stimulus (218, 260). In addition, animal studies using the Fos technique have shown that the number of Fos-labeled cells increases significantly in the parvocellular regions of the ventroposterior lateral and ventroposterior nuclei during noxious cardiac stimulation in conscious rats (3, 84). These particular regions project to the posterior, granular, and agranular insular cortex, which has been recognized as visceral sensory cortex (9, 56). The medial thalamus is primarily made up of the centralis lateralis and centrum medianum-parafascicularis nuclei (41, 215). The neurons in these nuclei relay information to the association cortex, including the insular cortex, amygdala, and cingulate gyrus (28, 29, 142, 303). Activation of these nuclei may primarily contribute to the motivational affective components of pain, including autonomic adjustments (2, 54, 217, 218). See reviews by Janig and Rosen for a more detailed discussion of the cortical processing (166, 294).

## Anxiety and the amygdala

Pain perception can be modulated by an aggregation of factors including mood, cognitive set, context, and neurochemicals. Perceived pain is particularly enhanced in people suffering from depression (259, 318) and anxiety (259). These symptoms are prevalent in patients suffering from angina-like pain with and without any evidence of ischemic heart disease (323). One region that may participate in these responses is the amygdala. The amygdala is one of the most likely candidates to heighten perceived pain by converting chronic stressful stimuli and anxiety into behavioral, visceral, and autonomic responses (300). The central nucleus of the amygdala contains glucocorticoid receptors responding to increased levels of corticosteroids that are released during anxiety and/or stress (322). Corticosteroids upregulate the expression of corticotropin-releasing factor and increase indices of anxiety (131, 322). Glucocorticoids implanted in the central nucleus of the amygdala produce hypersensitivity in visceromotor responses to colorectal distension (130) and

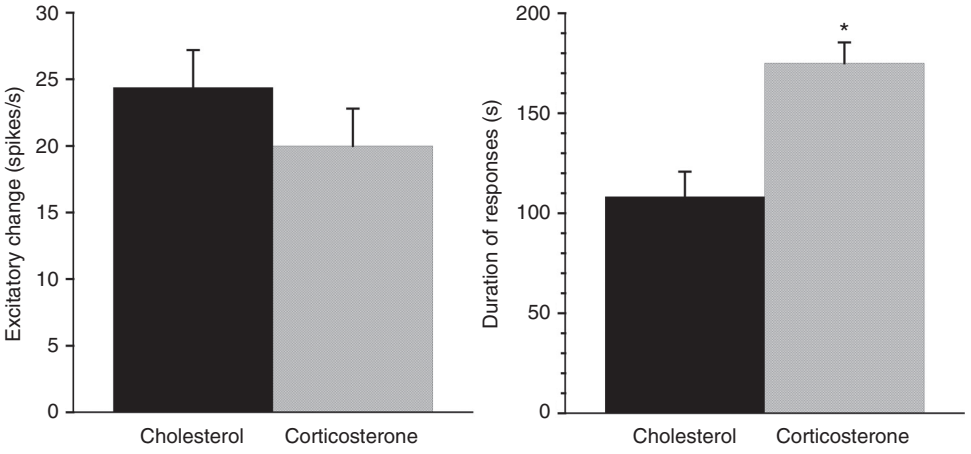



Figure 16 Responses of T3-T4 spinal neurons to intrapericardial injections of bradykinin (BK) in rats implanted with either corticosterone or cholesterol in the central nucleus of the amygdala. The duration of activity in response to BK was significantly longer in the corticosterone-implanted animals compared with cholesterol-implanted animals. Data are presented as mean ± SEM. $^*P < 0.05$.

sensitize lumbosacral spinal neurons to colorectal and urinary bladder distension (269, 270). These observations led to the idea that glucocorticoids in the amygdala might also modulate nociceptive input from the heart. Chronic activation of the amygdala with glucocorticoids was used to assess the effects of stress on the processing of information in the upper thoracic (T3-T4) spinal neurons and C1-C2 propriospinal neurons when the heart was exposed to nociceptive stimuli (110) (Fig. 16). Fisher 344 rats were selected for this study because these animals express a low level of anxiety-related behavior (131). Implants of micropellets containing crystalline corticosterone or cholesterol (30 μg, used as a control) were placed in the central nucleus of the amygdala. After 7 days, an elevated plus maze was used to show that animals implanted with corticosterone displayed high anxiety behavior when compared to animals with the cholesterol implants (322). To determine changes in processing of nociceptive information in the spinal cord, extracellular recordings were made from T3-T4 spinal neurons. Intrapericardial injections of the algesic chemical bradykinin were compared in corticosterone- and cholesterol-implanted rats. The duration of the responses from neurons to the noxious cardiac stimulus was significantly longer when compared to the duration of responses in the cholesterol-implanted animals. Additionally, neuronal activity in the corticosterone treated animals shifted from the short-lasting (the response lasts only as long as the stimulus is applied) to long-lasting excitatory (the response lasts well beyond the period the stimulus is applied) neurons (Fig. 17). The ratio of short lasting to long-lasting responses did not change in the cholesterol-treated animals. Generally, long-lasting excitatory neuronal activity is associated with hypersensitivity and intense pain; in contrast, short-lasting neuronal activity is associated with more acute responses. Another interesting observation was that the number of neurons with large receptive field sizes increased in the corticosterone-implanted but not the cholesterol-implanted animals, which is

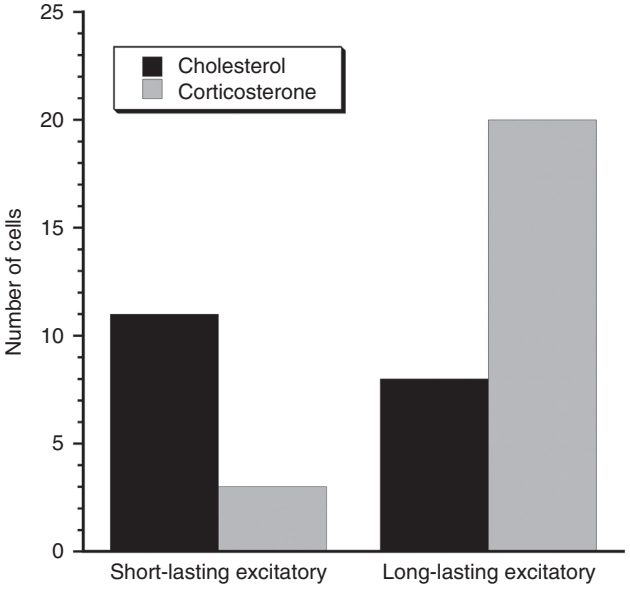
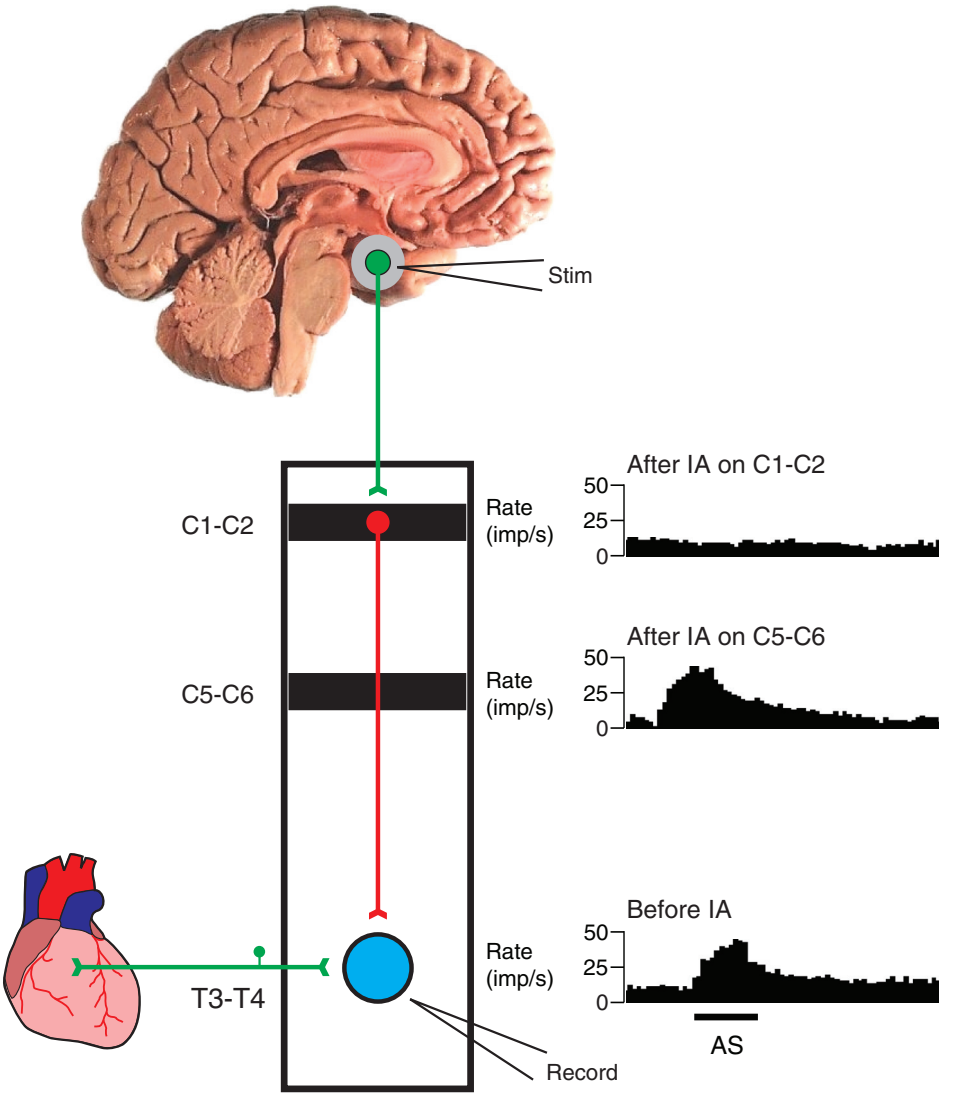



Figure 17 The number of T3-T4 spinal neurons with short-lasting excitatory and long-lasting excitatory responses to intrapericardial injections of bradykinin in rats implanted with either corticosterone or cholesterol in the central nucleus of the amygdala. Neurons with excitatory responses to bradykinin were subdivided into two groups based on the time of recovery to control activity after bradykinin was removed from the pericardial sac. Activity shifted from the short-lasting excitatory (e.g., the response lasts only as long as the stimulus is applied) to long-lasting excitatory (e.g., the responses lasts well beyond the period the stimulus was applied) classification in corticosterone-implanted animals.

another indication of sensitization. Thus, these results represent an important potential link between anxiety, which raises glucocorticoid levels in the central nucleus of the amygdala, and central sensitization to nociceptive input from the heart.

The potential role of the propriospinal pathway from C1-C2 segments in transmitting information from the amygdala to the thoracic spinal cord was determined by electrically




AS, stimulation in amygdala; IA, ibotenic acid; Stim, stimulation site; imp/s, neuronal discharge rate in impulses per second

Figure 18 Amygdala relay through the C1-C2 segments. The responses of neurons in the T3-T4 segments to stimulation of the amygdala were compared before (bottom panel on right) and after ibotenic acid was applied to either the C1-C2 or C5-C6 segments. Ibotenic acid placed on C5-C6 produced no diminution of response, but abolished the response if placed on C1-C2. Thus, the amygdala excites neurons in C1-C2, but not in C5-C6, that then inhibit responses of neurons in T3-T4.

stimulating the central nucleus of the amygdala. During the period of electrical stimulation, the extracellular potentials from T2-T4 spinal neurons increased (110). Ibotenic acid was then applied to the exposed C1-C2 and C5-C6 spinal cord segments, which disrupts cell function but does not affect axons. After C1-C2 cell disruption, responses of 65% of the T2-T4 cells tested by amygdala stimulation were eliminated. However, neuronal responses to amygdala stimulation were not affected after ibotenic acid was applied to the C5-C6 segments. The results lead to the suggestion that a C1-C2 propriospinal pathway, in part, transmits information from the amygdala to the T3-T4 neurons (Fig. 18).

## Syndrome X

The previous sections focused on anginal pain resulting from myocardial ischemia secondary to significant coronary artery disease. This section addresses cardiac syndrome X, which is used to describe patients who perceive angina-like pain with ST-segment depression during exercise induced angina, but their coronary arteries are normal as shown with angiography (187). Initially, the focus of attention was on coronary microvascular dysfunction since the hearts of the patients had no epicardial disease (51). Myocardial ischemia due to coronary microvascular dysfunction has been suggested to be a major cause of the syndrome (52, 187, 241). In addition,

results from the Women's Ischemia Syndrome Evaluation study has led to the suggestion that dysfunctional microcirculation may be the cause of syndrome X in a group of women (284). However, several studies have also led to the suggestion that abnormal pain perception may also contribute to this syndrome (237, 254, 293, 298). The supporting evidence includes patients with syndrome X experiencing a lower threshold for cardiac pain during pharmacological stress or tending to complain more frequently and had increased painful sensitivity to electrical stimulation of the ventricle during pacing (97, 255, 298).

Functional neuroimaging studies have shown that patients with cardiac syndrome X but not controls exhibit activation of the right anterior insula cortex during high-dose dobutamine infusion that induced angina and ST segment changes but no abnormalities in left ventricular wall motion. (297) These authors suggested that altered cerebral cortical activity may modulate the input coming into the spinal cord from the cardiac afferent fibers. Further support for suggesting that cardiac syndrome X may result from central neural origin comes from reports showing that direct electrical stimulation of the human insula, operculoinsular cortex, and thalamus elicits pain and/or angina like pain (115, 190, 243). However, hypersensitive cardiac nociceptors, abnormal transmission, and processing of the pathways that transmit the information to subcortical levels and/or modulation of the nociceptive impulses at the subcortical levels may also contribute to the abnormal activation of different regions of the cerebrum.

## Silent myocardial ischemia

The emphasis of this review has been a description of mechanisms that ultimately lead to the sensations of typical or atypical angina. However, some patients do not feel anginal pain during myocardial ischemia. Ambulatory electrocardiography used to monitor patients with stable angina have shown that approximately 40% to 50% of these patients have episodes of silent myocardial ischemia (70, 290, 313). It is interesting to note that these episodes continue to happen even when antianginal agents are being used to treat these patients (82).

This phenomenon is termed silent myocardial ischemia, and is defined as the absence of angina-like symptoms when objective evidence predicts that that the patient should be experiencing cardiac pain or angina pectoris. Gutterman (133) and Cohn et al. (71) have written excellent reviews about prevalence, diagnosis, possible mechanisms, and alternative theories of silent myocardial ischemia, which will not be detailed in this article, but is highly recommended for understanding the clinical components of this subject in more detail.

Explanations for silent myocardial ischemia can be loosely categorized into three theories. These theories are the following: (i) global deficiency in pain perception; (ii) anatomical and functional changes in nociceptors and nerves; and (iii) the intensity theory which postulates that more prolonged and intense episodes of myocardial ischemia result in angina pectoris, but silent ischemia results from shorter and/or less intense episodes (133). All of these theories may contribute to episodes of silent ischemia but this discussion will focus primarily on global deficiency in pain perception.

Earlier we noted that there is a difference in the distribution of vagal and spinal afferents in the heart. Activation of vagal afferents particularly from the inferior-posterior region of the left ventricle may contribute to the global deficiency in pain perception. Droste and Rosskamm (94) addressed this theory by conducting a study in humans. Using exercise as the stressor they identified 22 patients who experienced angina pectoris with ST depression and 20 who had depressed ST changes but had silent myocardial ischemia. Upon further examination asymptomatic patients more frequently had stenosis in the left circumflex coronary artery or right coronary artery. In addition, these patients had abnormal wall movement localized to the posterobasal or diaphragmatic region of the left ventricle, which also evokes vagal reflexes. In contrast, patients who experienced the symptoms of angina pectoris more commonly had stenosis of the left anterior descending artery from which sympathetic reflexes are activated. In summary, silent myocardial ischemia may occur because myocardial ischemia localized to the inferior-posterior region of the left ventricle preferentially activates vagal afferent fibers.

Patients with asymptomatic episodes of myocardial ischemia also appear to have a defective warning system of somatic pain. Somatic pain perception was compared in patients with silent myocardial ischemia and with angina pectoris; both groups exhibited significant ST segment depression during stress tests using exercise (93, 94, 99, 128, 257). Nociceptive modalities including electric shock, cold pressor stimulation, dental pulp stimulation, and tourniquet-induced forearm ischemia were used to determine somatic pain perception. A comparison of the two groups of patients showed that patients with silent myocardial ischemia had a significantly higher pain threshold and greater tolerance to these nociceptive modalities compared to the thresholds and tolerance in patients who were symptomatic to myocardial ischemia.

Furthermore, it was speculated that vagal afferent activation might be one of the mechanisms that produce silent myocardial ischemia in some patients (133). As pointed out in the previous paragraph asymptomatic patients with silent ischemia had higher pain thresholds during dental pulp stimulation (100). In support of vagal activation increasing somatic thresholds, animal studies showed that vagal afferent stimulation suppressed the activity of C1 neurons that responded to tooth pulp stimulation (338). A population of C1 neurons primarily in the superficial dorsal horn is part of the population of caudal trigeminal neurons that innervated the teeth stimulated in this study. While reduction of tooth pulp stimulation via vagal stimulation may provide at least one mechanism for increasing pain threshold, it does not explain how vagal stimulation contributes to the defective warning system that affects somatic pain in other parts of the body.

A brief discussion will be provided to address the possibility that changes in nerve conduction, particularly in the sympathetic nerves, can contribute to silent myocardial ischemia. A new theory has been proposed that involves the concept of "neural stunning" (133). The idea behind this theory is that a brief episode of myocardial ischemia that results in angina pectoris evokes a temporary suppression of conduction in the sympathetic nerves that lasts long enough to cause silent myocardial ischemia in subsequent episodes of ischemia. This theory is supported by the fact that the activity of sympathetic efferent nerves is temporarily reduced during brief episodes of myocardial ischemia and the subsequent reperfusion phase (69, 134). The increased release of adenosine, hydrogen ion, and potassium in the ischemic zone appears to contribute to the reduction in sympathetic nerve conduction (229).

In addition to neural stunning of the sympathetic efferent fibers, the cardiac spinal afferent fibers also are affected. Single unit activity of A-delta and C fibers increased their activity to mechanical and chemical stimuli as well as one minute of coronary artery occlusion (1). However, the one minute coronary artery occlusion significantly reduced afferent activity if it followed a 15-min occlusion and 15 min of reperfusion. These results supported the idea that brief episodes of myocardial ischemia can suppress mechanosensitive and ischemia-sensitive activity of cardiac spinal afferent fibers. Additionally neural stunning of these fibers also contributes to silent myocardial ischemia. However, this theory would not necessarily explain the global reduction in pain sensitivity, which is more readily explained by the role the vagal afferents play in contributing to silent myocardial ischemia.

Based on the evidence presented on central processing of cardiac nociceptive information, we propose the following. Typical angina is mediated by spinal cardiac afferents that activate STT and SRT neurons (107). These neurons relay noxious cardiac information to the thalamus and brainstem, respectively, and ultimately to the cerebral cortex. In the cortex, information is interpreted as cardiac pain with the somatic referral characteristic of typical angina because the somatic receptive fields of upper thoracic STT and SRT neurons are similar to the regions of referred pain. In contrast, cardiac vagal afferents mediate atypical angina because the somatic receptive fields of upper cervical STT neurons excited by vagal afferents resemble the regions of referred pain for atypical angina. Since spinal and vagal afferents are not evenly distributed across the myocardium, whether a patient experiences typical or atypical angina probably depends on which region of the heart becomes ischemic because spinal or vagal afferents may be preferentially activated. Silent myocardial ischemia occurs primarily as a result of cardiac vagal afferents exciting descending propriospinal neurons in the C1-C2 segments that inhibit STT and SRT neurons in the upper thoracic segments, thereby attenuating the ascending cardiac nociceptive information. Different emotional states or other behaviors can influence the sensations of angina through pathways including the amygdala, SC-PB region, and raphespinal tract, and probably others. It should also be noted that a series of studies have also shown that patients with diabetic autonomic neuropathy have a greater prevalence of silent myocardial ischemia (355).

## Cross-Organ Communication

The previous sections have shown that viscerosomatic referral and sensitization of spinal neurons and cells of origin of ascending pathways resulting from ischemic heart disease have been widely investigated and well-documented clinically. However, viscero-visceral referral and cross-organ sensitization have only recently been identified as making important contributions to visceral disease states. Diagnosing cardiac pain based on the referral of pain to the chest can be misleading because of the viscero-visceral interactions. The focus of this section will be on the interactions between the heart and esophagus and the heart and gallbladder because they have been studied in more detail than other organs.

Understanding sensitization that results from viscero-visceral interactions is important for two reasons. First, this type of pain gives rise to intricate and complex clinical conditions that are challenging for making an appropriate diagnosis. Second, it is important to address therapeutic implications, because the possibility exists that modulating referred pain to somatic structures of one diseased organ may affect the pain that originates from another organ.

### Heart and esophagus

We will begin with consideration of interactions between the esophagus and heart. Gastroesophageal reflux disease (GERD) is a common esophageal disorder that usually results from repeated reentrance of stomach contents to the esophagus. This disorder affects approximately 19 million people in the United States (46, 80, 114, 306). GERD typically presents as heartburn and/or acid regurgitation; however, extraesophageal presentations in patients can occasionally appear to mimic angina-like pain that is commonly associated with ischemic heart disease (100, 168, 205, 289). Several studies have shown that GERD is associated with ischemic heart disease (86, 144, 196, 330). For example, esophageal insults can significantly reduce coronary blood flow velocity and volume, generate cardiac arrhythmias, elicit ischemic ECG changes, and produce typical angina-like pain in patients with ischemic heart disease (27, 67, 68, 216, 291, 320, 372). In addition, GERD patients who do not have ischemic heart disease often have chest pain that mimics angina (203). One study reported that 20% to 50% of patients with non-ischemic chest pain have esophageal abnormalities (67). Also, 46% of patients with normal coronary angiograms and chest pain have been found to have GERD (314). Human studies have shown that esophageal acid alters sensory perception, in particular, resulting in chest pain that has been

attributed to central sensitization of dorsal spinal neurons (91, 92, 159, 258, 283, 307-310). One human study suggested that the mechanism underlying esophageal hyperalgesia may be due to increased spinal viscereoreceptive excitability (spinal sensitization) of spinal dorsal horn neurons, but animal studies were not available to support their argument (149). Very few animal studies have considered the effects of acid sensitivity or the components of GER on spinal neurons. We and others have experimentally examined the innervation as well as the afferent pathways and spinal processing of esophageal mechanical stimulation in animal models (98,263,264). However, very little is known about spinal neuronal response characteristics to esophageal distension when specific "natural" chemical stimuli are administered directly into the esophagus prior to and during the distension period (119, 201, 266, 319).

Cross-organ communication between the esophagus and other organs such as the heart and lungs most likely depends on the innervation by the vagus and visceral spinal afferent fibers. Research results have shown that nociceptive afferent information from these organs is transmitted predominantly through spinal visceral nerves and converges onto spinal neurons in the same segments of the thoracic spinal cord (263, 268). Convergence of afferent input from an inflamed organ onto a spinal neuron with afferent input from "unaffected" organs might contribute to sensitization and difficulty ascribing the origin of pain to a given organ.

Convergence of spinal afferents from the esophagus and heart onto thoracic spinal neurons can provide a neural substrate to mediate viscera-visceral nociception and reflexes. To mimic the clinical situation in which the chest pain originated from the esophagus, a study was conducted to compare the excitability and responsiveness of spinal neurons of the upper thoracic segments that receive noxious cardiac input in anesthetized rats with and without GER (272) (Fig. 19). In acute experiments, the gastric fundus and pyloric ligations as well as a longitudinal myelotomy at the gastroesophageal junction were performed to induce acute GER. After waiting for approximately 4 to 9 h after GER surgery was completed, recordings of extracellular potentials from single neurons were made from the dorsal gray matter of the T3 spinal segment. To activate cardiac nociceptors, injections of bradykinin were made into the pericardial sac. In addition, distensions of the esophagus with a balloon were used to activate esophageal afferent fibers. Several interesting observations were made to demonstrate that GER can impact the processing of nociceptive information from the heart (272). First, significantly more spinal neurons in the GER group responded to intrapericardial bradykinin injections compared to the control group. Second, the proportion of cardiac responsive neurons in the superficial spinal gray laminae of GER animals was significantly lower from the neurons located in the deeper laminae of the dorsal horn, but no differences were observed in control animals. Third, excitatory responses of spinal neurons to intrapericardial bradykinin injections in the GER group were significantly greater than the responses observed in the control group (Fig. 19). Fourth, 95.7% spinal neurons responded to cardiac

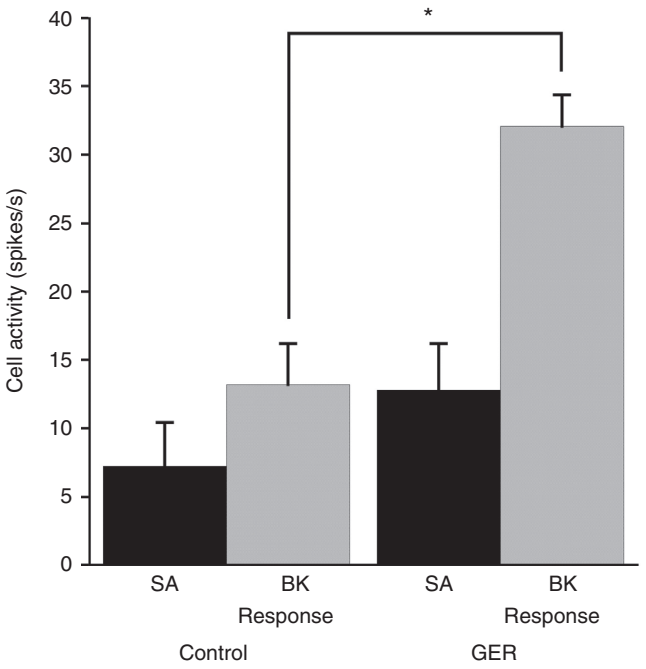



Figure 19 Effects of intrapericardial injection of bradykinin (BK) on neurons in the T3 segment of the rat spinal cord. Solid bars represent the spontaneous activity of neurons in rats with gastroesophageal reflux (GER) or surgical controls. Hatched bars represent the cell activity following injection of BK into the pericardial sac in rats with GER and surgical controls. Results indicate that neuronal responses to intracardiac BK were greater in rats with GER. Data are presented as mean ± SEM. $^{*}P < 0.05$. (Reprinted, with permission, from 272.)

input and esophageal distension in the GER group, which was significantly higher than the number of neurons that responded in the control group (61.5%). Thus, this study provided important evidence that acute esophageal inflammation induced by gastric reflux in rats enhanced the viscereoreceptive sensitivity of upper thoracic spinal neurons receiving spinal afferent inputs from the heart. The cross-organ sensitization of spinal neuronal processing observed in this study could mediate pathophysiological viscero-visceral communication in patients with cardiac and noncardiac chest pain. Thus, even though chest pain can result independently from ischemic heart disease or GERD, there can also be a clinically significant interaction between cardiac disease and esophageal disorders. For example, GERD and ischemic heart disease often coexist and may further interact to produce and/or exacerbate chest pain and other symptoms (86, 144, 196, 325, 330).

## Heart and gallbladder

Next, we will consider interactions between the heart and gallbladder. Gallbladder disease usually generates episodes of pain that are referred to the abdomen or back (324). However, in some patients angina-like pain may also be referred

to the chest (137, 224, 279, 280). In fact, cholecystectomies occasionally relieve angina-like pain (130). Human studies have shown that experimentally distending the gallbladder or biliary ducts may elicit angina-like pain and ECG changes (211,280). In addition, gallbladder and biliary duct distension or application of algesic chemicals to the gallbladder reduce coronary blood flow (78), change heart rate (78,150,242) and ECG configuration (150), or increase indices of contractility (242). Human studies have also shown that patients with ischemic heart disease and cholecystitis experience more frequent episodes of angina when compared to patients with ischemic heart disease alone (126), and men with a history of angina are significantly more likely to develop biliary stones (104). Collectively, this information suggests that there is a powerful interplay between the heart and the gallbladder.

Mechanisms of viscero-visceral hyperalgesia for the heart and gallbladder most likely depend on increased nociceptive input from one organ that sensitizes viscero-viscero-somatic convergent neurons in the central nervous system. Thus, information coming from the second visceral location and from the somatic areas of referral would be facilitated. As will be discussed below, both animal and human studies demonstrate viscero-viscero-somatic convergence onto spinal neurons between these two organs.

The first section will demonstrate in animal studies that nociceptive afferent fibers from the gallbladder converge onto spinothalamic tract cells of the upper thoracic spinal segments receiving nociceptive afferent input from the heart. The second section will provide information from human studies that viscero-visceral interactions between the heart and gallbladder can enhance the chest pain associated with ischemic heart disease and cholecystitis.

In animal studies, electrical stimulation of the splanchnic nerve excites approximately 75% of upper thoracic STT neurons, and these same cells are also excited by convergent input resulting from electrical stimulation of the cardiopulmonary afferent fibers (12). These STT cells also receive somatic afferent information from mechanical manipulation of the skin and muscle located on the chest and upper forearm. However, gallbladder distensions to nociceptive intensities excited approximately only 35% of the STT cells of the upper thoracic segments (13). Thus, splanchnic nerve stimulation may have also activated visceral spinal afferent fibers from other abdominal organs. An interesting observation was that 90% of the gallbladder-responsive cells and only approximately 50% of the gallbladder-unresponsive STT cells increased the discharge rate after the algesic chemical, bradykinin, excited nociceptive spinal afferents from the heart. It was also noted that the peak discharge rates of the gallbladder-responsive cells to bradykinin were significantly greater than the rates observed from the gallbladder unresponsive neurons (13) (Fig. 20). Another interesting observation was that gallbladder distension only excited and never inhibited T1-T5 STT cells. In contrast gallbladder distension both excited and inhibited upper thoracic dorsal horn neurons with unknown projection sites in the cat (15). The difference in the two studies most likely reflects the populations of neurons studied. For example, a population of interneurons may participate in complex neural networks that involve reflex responses associated with nociceptive stimuli. The fact that gallbladder distension only excited STT cells is consistent with the generally held concept from somatic studies that increased activity of these neurons leads to painful sensations (108, 192, 369) and with the clinical observations that increased pressure in the gallbladder pressure coincides with pain (77, 324).

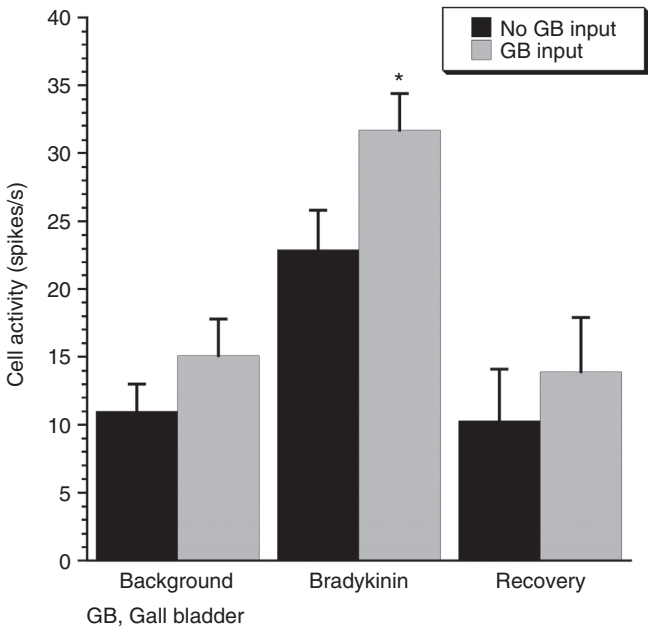



Figure 20 Responses of gallbladder-responsive cells and nonresponsive cells to injection of bradykinin (BK) into the left atrium. Values represent the cell activity of cells with gallbladder input (GB input) or no gallbladder input (no GB input). BK values represent peak activity during responses. Results indicate that cells receiving GB input had more robust responses to BK than cells without GB input. $^{*}P < 0.05$ compared with cells without gallbladder input. (Adapted, with, permission from 13.)

Viscerosomatic and viscero-visceral referred pain may occur because the spatial pattern of referred visceral pain and hyperalgesia is dependent upon the same segmental projections or largely overlapping projections of their spinal afferent fibers projecting to the dorsal horn (167). This hypothesis was examined in an animal model (12). Transection of the sympathetic chain between segments T5-T6 eliminated approximately 25% of responses of the upper thoracic STT cells to electrical stimulation of the splanchnic nerve. More caudal transections of the sympathetic chain reduced the cells' responses until approximately 70% of splanchnic stimulation was eliminated after a transection was made between the T8 and T9 rami communicates. However, lesions of the lateral and ventrolateral white columns, but not the dorsolateral columns at segments T5-T6, reduced or abolished the spinothalamic tract cell responses to splanchnic nerve stimulation. These results lead to the suggestion that at least for splanchnic afferent input propriospinal pathways and to a less

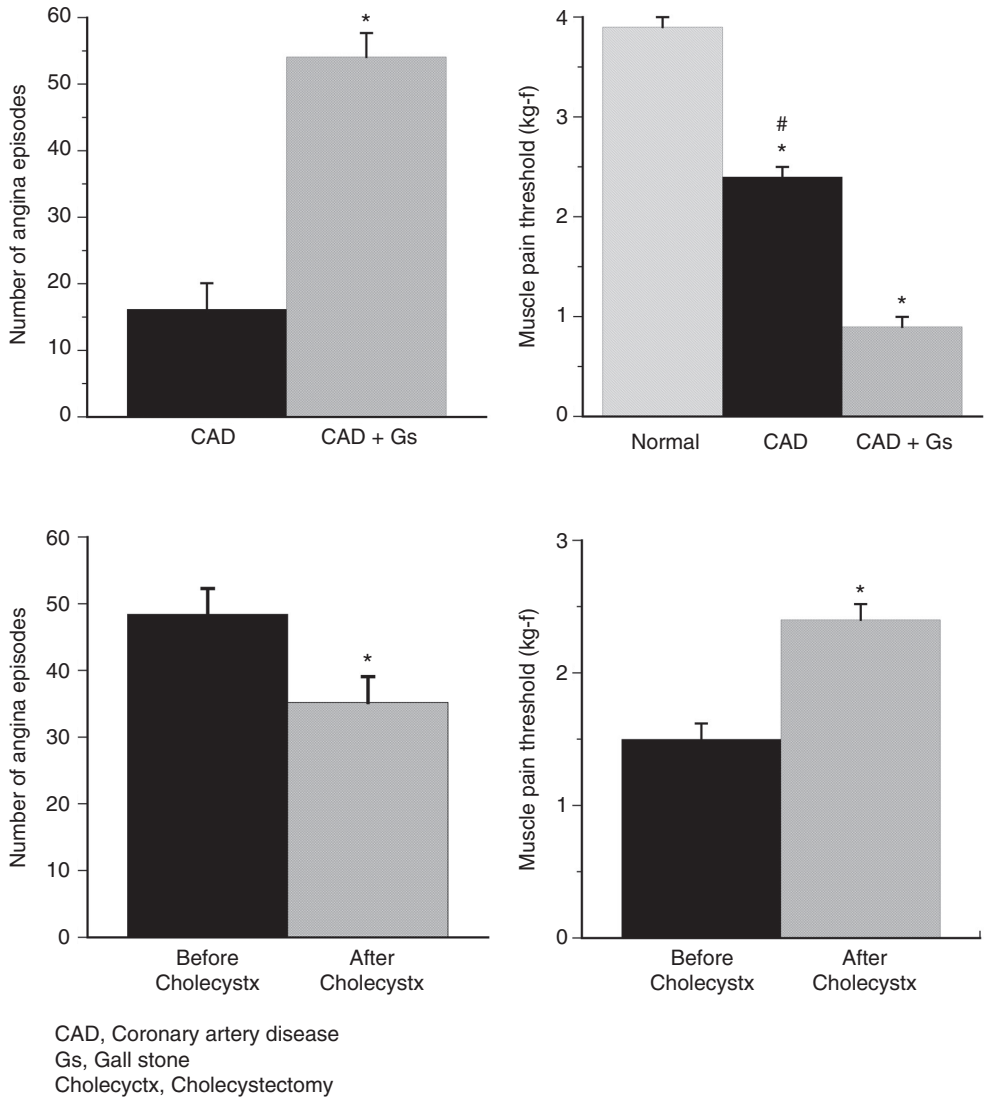



Figure 21 Heart gallbladder interactions. Upper panels: (left) Cardiac symptoms over 1 month in patients with coronary artery disease (CAD) and patients with coronary artery disease + gallbladder stone (CAD + Gs). Results indicate that patients were more likely to experience angina if they had a gallstone. (Right) Pressure pain thresholds (PPTs) in the left anterior chest area in healthy subjects (normal), and two groups of patients with either CAD only or CAD + Gs presenting a comparable number of angina episodes in the preceding month. Compared to normals, patients with CAD had lower PPTs, and patients with CAD and Gs experienced a greater lowering of PPT compared to CAD. Lower panels: (left) Cardiac symptoms for 1 month before (before Cholecystx) and 1 month after cholecystectomy (after Cholecystx). Removal of the stone significantly reduced the number of angina episodes. (Right) PPTs in the chest area before and after the operation in CAD + Gs patients. Removal of the stone increased the PPT. Note: The upper right CAD + Gs group is the same as the lower right before Cholecystx group; mean values are different because there was one less patient in the lower right group. Overall results suggest that the greater the number of visceral organs with pathology, the greater the likelihood of experiencing pain from any single organ. (Adapted, with permission, from 126.)

extent the sympathetic chain play an important role in transmitting information from the splanchnic nerve to the upper thoracic segments (18, 89, 90).

Gallbladder distensions using pressures ranging between 10 and 100 mmHg are effective for activating the upper thoracic STT cells as well as lower thoracic neurons with unidentified projections (13, 15, 58). Approximately 50 mmHg is the average pressure necessary to activate the upper thoracic STT cells. This pressure coincides with gallbladder pressures that are generated with acute cholecystitis (13). These higher pressure requirements support the idea that this distension pressure is noxious.

It is also important to note that all STT cells with viscero-visceral convergence had somatic receptive fields located in the chest region. The fact that gallbladder distension excited more than one-third of the upper thoracic STT cell may

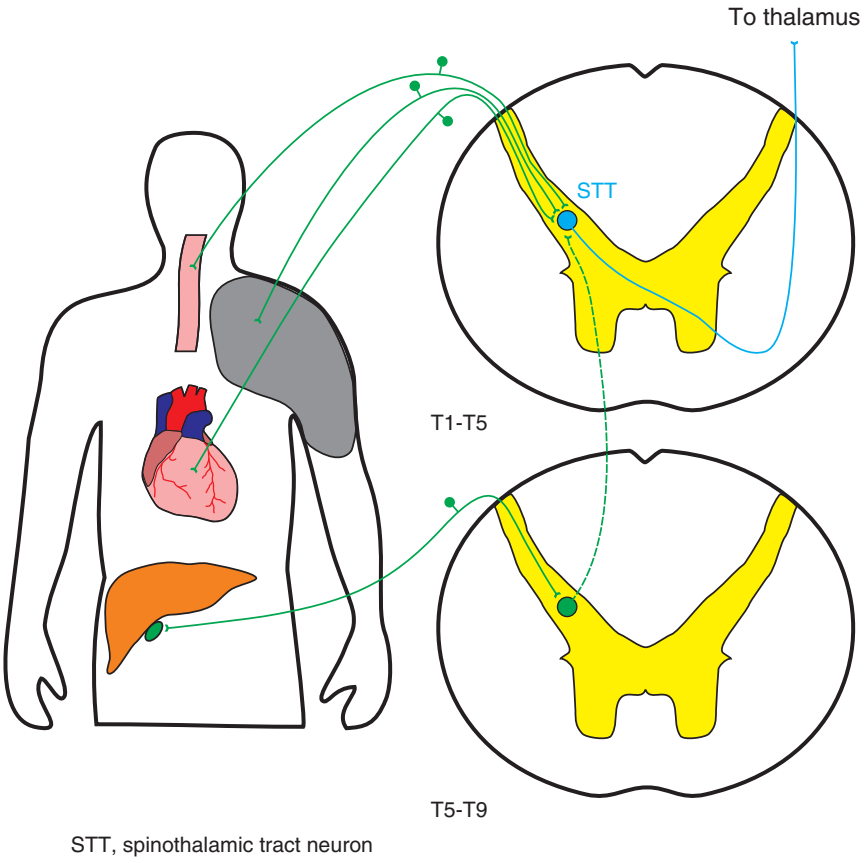



Figure 22 Multi-organ convergence onto spinothalamic tract neurons. Spinothalamic tract neurons in the upper thoracic segments receive converging nociceptive inputs from the heart, esophagus, and gallbladder, along with somatic input from the chest and upper arm. The dashed line indicates that the precise pathway by which gallbladder input reaches the upper thoracic cord has not been identified.

explain why some patients with acute inflammatory gallbladder disease may experience pain referral in the chest in addition to the more usual sites of pain, such as the abdomen or back (324). The possibility that this type of chest pain, in some patients, may result from reflexes which alter cardiac performance, thus leading to true myocardial ischemia, cannot be dismissed. However, these observations seem to be more consistent with the clinical studies showing that some patients who experience chest pain associated with gallbladder disease that are myocardial ischemia related (137, 224).

Giamberardino et al. (126) in their elegant human study characterized different clinical models to demonstrate the importance of viscero-visceral hyperalgesia in determining the appropriate clinical outcome. Although their study examined cross organ communication among several visceral organs, we will focus on patients experiencing only symptomatic ischemic heart disease or patients with symptomatic ischemic heart disease plus symptoms resulting from stones in the gallbladder. Vigorous inclusion criteria were used to determine the status of the patients: (i) patients with ischemic heart disease were diagnosed with angiography and had to fall into the Class III or IV for angina symptoms; (ii) these symptoms caused patients to have marked or severe limitations in their daily activities; (iii) patients were negative for gallbladder stones assessed by abdominal ultrasounds; and (iv) was essential that angina-like pain was referred to the left anterior chest region to establish a consistent area that can be used to determine muscle pressure pain thresholds in these patients. To demonstrate viscero-visceral interactions, another group of patients was required to be symptomatic for both coronary artery disease and gallbladder calculosis with the pain projected to the upper right abdominal quadrant. For one month, the patients were required to record their typical angina episodes and the intensity of these episodes using visual analog scales. At the end of the month, patients were measured for muscle electrical pain thresholds in the left anterior chest region. The results showed that anginal episodes were significantly more frequent in patients with both coronary artery disease and gallbladder calculosis when compared to patients with only coronary artery disease (Fig. 21). In addition, patients with both diseases experienced significantly higher pain intensities. Furthermore the patients with both

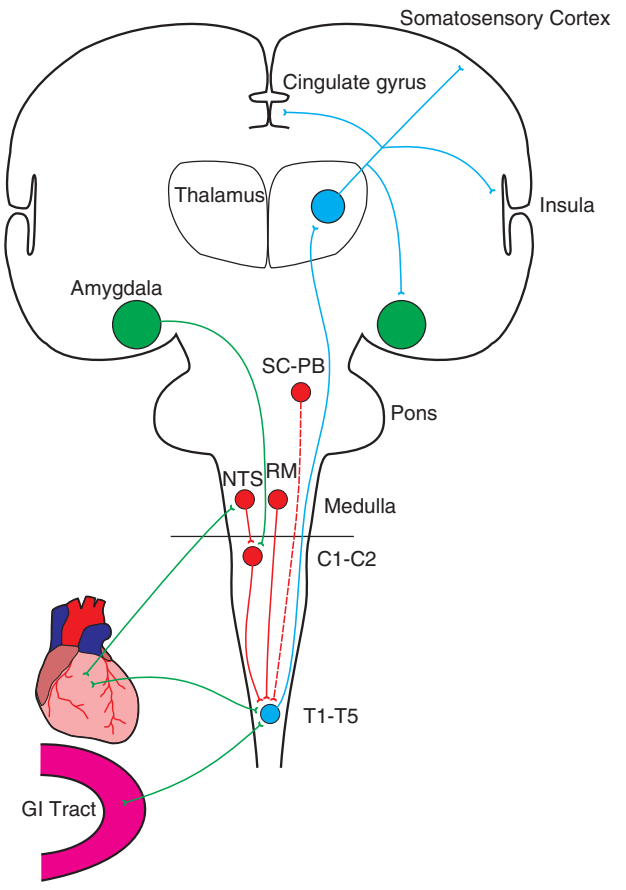
diseases had pressure pain thresholds in the chest that were significantly lower than normal patients and patients with only coronary artery disease.

An important component of the Giamberardino study (126) was that the same symptoms were reevaluated at the appropriate time after a group of patients with both ischemic heart disease and gallbladder calculosis had undergone cholecystectomy surgery. Measurements taken a month after surgery showed that the number and intensity of the angina episodes were reduced significantly when compared to the measurements taken the month prior to the surgery. Furthermore, after cholecystectomy the pressure pain thresholds of the anterior chest were increased significantly when compared to the values taken prior to surgery. The results of the study by Giamberardino et al. (126) show that viscero-visceral hyperalgesia can occur at different visceral levels in patients. Furthermore, both the spontaneous visceral pain symptoms and the referred muscle hyperalgesia can be enhanced because of the interaction between heart and gallbladder. An exciting observation of this study was that the treatment of the painful episodes for one organ decreases the symptoms of not only that organ but also the symptoms from the other location. Figure 22 presents a conceptual diagram for multi-organ convergence onto STT neurons.

Results of the studies in animal models and humans provide important diagnostic as well as therapeutic implications for treating angina pain as well as other types of visceral pain. The first implication is that when patients present with particularly intense and/or frequent episodes of visceral pain, physicians should systematically explore inputs from another organ, particularly if the two organs have overlapping innervation, to make an appropriate diagnosis (126). The second implication is that treating typical pain from one visceral organ may occasionally be accomplished by treating the disease in another visceral organ (126). Thus, these basic and clinical studies expand the range of potentially effective and not merely symptomatic therapies for anginal pain. Furthermore, treatment of pain arising from one organ can affect pain sensitivity arising from the other organ. In other words cardiac revascularization or cholecystectomy can relieve the symptoms originating not only from the organ on which the intervention was performed but also from the convergent organ.

## Conclusions

Figure 23 presents a conceptual diagram of the pathways discussed in this review that can affect cardiac nociceptive processing in the upper thoracic spinal cord and ultimately produce the various patterns of chest pain experienced in different patients. Convergence of cardiac, somatic, and gastrointestinal inputs onto a common pool of STT neurons provides a neurophysiological and neuroanatomical basis for pain referral to the chest and/or upper arm resulting from nociceptive stimuli originating from the heart or gastrointestinal tract.




NTS, nucleus tractus solitarius; SC-PB, region near the locus coeruleus and parabrachial nucleus; RM, raphe magnus

Figure 23 Summary of major visceral pathways influencing spinothalamic tract neuronal activity described in this review. For description, see the concluding paragraph.

Activation of cardiac vagal afferents may produce somatic pain referral to the neck by virtue of viscerosomatic convergence onto STT neurons in the C1-C2 segments via a relay through the NTS, or lead to silent ischemia by exciting a propriospinal pathway that inhibits STT neurons in the upper thoracic segments. Descending pathways from the NRM and subcoeruleus-parabrachial region inhibit responses of upper thoracic STT neurons to nociceptive input arising from the heart, but descending input from the amygdala facilitates STT neuronal responses to nociceptive cardiac input. STT input is relayed not only to the somatosensory cortex, but also to the cingulate gyrus, insula, and amygdala. These complex projections provide bases for different emotional behaviors to influence the experience of angina as well as for cardiac nociception to influence autonomic responses. The complex interplay among all of these pathways, as well as pathways that have not been well-studied to date, likely explains why the experience and presentation of anginal symptoms varies in different patients. Much work remains to be conducted to understand the mechanisms involved in visceral pain referral to the upper part of the body.

# References


1. Abe T, Morgan D, Sengupta JN, Gebhart GF, Gutterman DD. Attenuation of ischemia-induced activation of cardiac sympathetic afferents following brief myocardial ischemia in cats. *J Auton Nerv Syst* 71: 28-36, 1998.
2. Albe-Fessard D, Besson JM. Convergent thalamic and cortical projections. The non-specific system. In: Iggo A, editor. *Handbook of Sensory Physiology*. Berlin: Springer-Verlag, pp. 489-560, 1973.
3. Albutaihi IA, Hautvast RW, DeJongste MJ, Ter Horst GJ, Staal MJ. Cardiac nociception in rats: Neuronal pathways and the influence of dermal neurostimulation on conveyance to the central nervous system. *J Mol Neurosci* 20: 43-52, 2003.
4. Al-Chaer ED, Feng Y, Willis WD. Comparative study of viscerosomatic input onto postsynaptic dorsal column and spinothalamic tract neurons in the primate. *J Neurophysiol* 82: 1876-1882, 1999.
5. Al-Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology* 119: 1276-1285, 2000.
6. Al-Chaer ED, Lawand, NB, Westlund, KN, Willis, WD. Pelvic visceral input into the nucleus gracilis is largely mediated by the postsynaptic dorsal column pathway. *J Neurophysiol* 76: 2675-2690, 1996.
7. Al-Chaer ED, Lawand NB, Westlund KN, Willis WD. Visceral nociceptive input into the ventral posterolateral nucleus of the thalamus: A new function for the dorsal column pathway. *J Neurophysiol* 76: 2661-2674, 1996.
8. Al-Chaer ED, Westlund KN, Willis WD. Sensitization of postsynaptic dorsal column neuronal responses by colon inflammation. *NeuroReport* 8: 3267-3273, 1997.
9. Allen GV, Saper CB, Hurley KM, Cechetto DF. Organization of visceral and limbic connections in the insular cortex of the rat. *J Comp Neurol* 311: 1-16, 1991
10. Ammons WS, Blair RW, Foreman RD. Vagal afferent inhibition of primate thoracic spinothalamic neurons. *J Neurophysiol* 50: 926-940, 1983.
11. Ammons WS, Blair RW, Foreman RD. Vagal afferent inhibition of spinothalamic cell responses to sympathetic afferents and bradykinin in the monkey. *Circ Res* 53: 603-612, 1983.
12. Ammons WS, Blair RW, Foreman RD. Greater splanchnic excitation of primate Tl-T5 spinothalamic neurons. *J Neurophysiol* 51: 592-603, 1984.
13. Ammons WS, Blair RW, Foreman RD. Responses of primate T1-T5 spinothalamic neurons to gallbladder distension. *Am J Physiol* 247: R995-R1002, 1984.
14. Ammons WS, Blair RW, Foreman RD. Raphe magnus inhibition of primate T1-T4 spinothalamic cells with cardiopulmonary visceral input. *Pain* 20: 247-260, 1984c.
15. Ammons WS, Foreman RD. Cardiovascular and T2-T4 dorsal horn cell responses to gallbladder distention in the cat. *Brain Res* 321: 267-277, 1984.
16. Ammons WS, Girardot M-N, Foreman RD. T2-T5 spinothalamic neurons projecting to medial thalamus with viscerosomatic input. *J Neurophysiol* 54: 73-89, 1985.
17. Ammons WS, Girardot M-N, Foreman RD. Effects of intracardiac bradykinin on T2-T5 medial spinothalamic cells. *Am J Physiol* 249: R147-R152, 1985.
18. Bain WA, Irving JT, McSwiney BA. The afferent fibres from the abdomenn in the splanchnic nerves. *J Physiol (Lond)* 84: 323-333, 1935.
19. Baker DG, Coleridge HM, Coleridge JCG. Vagal afferent C fibres from the ventricle. In: Hainsworth R, Kidd C, Linden RJ, editors. *Cardiac Receptors*. Cambridge: Cambridge University Press, pp. 117-137, 1979.
20. Baker DG, Coleridge HM, Coleridge JCG, Nerdrum T. Search for a cardiac nociceptor: stimulation by bradykinin of sympathetic afferent nerve endings in the heart of cat. *J Physiol* 306: 519-536, 1980.
21. Beal MC. Viscerosomatic reflexes: A review. *J Am Osteopath Assoc* 85: 786-801, 1985.
22. Beall JE, Martin RF, Applebaum AE, Willis WD. Inhibition of primate spinothalamic tract neurons by stimulation in the region of the nucleus raphe magnus. *Brain Res* 114: 328-333, 1976.
23. Becker R, Sure U, Bertalanffy H. Punctate midline myelotomy. A new approach in the management of visceral pain. *Acta Neurochir (Wien)* 141: 881-883, 1999.
24. Beckstead RM, Morse JR, Norgren R. The nucleus of the solitary tract in the monkey: Projections to the thalamus and brainstem nuclei. *Comp Neurol* 190: 259-282, 1980.
25. Beckstead RM, Norgren R. An autoradiographic examination of the central distribution of the trigeminal, facial, glossopharyngeal, and vagal nerves in the monkey. *Comp Neurol* 184: 455-472, 1979.
26. Bennett GJ. Update on the neurophysiology of pain transmission and modulation: Focus on the NMDA-receptor. *J Pain Symptom Manage* 19: S2-S6, 2000.
27. Bennett JR, Atkinson M. The differentiation between oesophageal and cardiac pain. *Lancet* 2: 1123-1127, 1966.
28. Bentivoglio M, Macchi C, Albanese A. The cortical projections of the thalamic intralaminar nuclei as studies in cat and rat with the multiple-fluorescence retrograde tracing technique. *Neurosci Lett* 26: 5-10, 1981.
29. Berendse HW, Groenewengen VH. Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat. *Neuroscience* 42: 173-102, 1991.
30. Berger HJ, Zaret BL, Speroff L, Cohen LS, Wolfson S. Cardiac prostaglandin release during myocardial ischemia induced by atrial pacing in patients with coronary artery disease. *Am J Cardiol* 39: 481-486, 1977.
31. Berger UV, Hediger MA. Distribution of the glutamate transporters GLAST and GLT-1 in rat circumventricular organs, meninges, and dorsal root ganglia. *J Comp Neurol* 421: 385-399, 2000.
32. Berkley KJ, Hubscher CH. Are there separate central nervous system pathways for touch and pain? *Nat Med* 1: 766-773, 1995.
33. Besson JM, Chaouch A. Peripheral and spinal mechanisms of nociception. *Physiol Rev* 67: 67-186, 1987.
34. Blair RW, Ammons WS, Foreman RD. Responses of thoracic spinothalamic and spinoreticular cells to coronary artery occlusion. *J Neurophysiol* 51: 636-648, 1984.
35. Blair RW, Evans AR. Responses of medullary raphespinal neurons to electrical stimulation of thoracic sympathetic afferents, vagal afferents, and to other sensory inputs in cats. *J Neurophysiol* 66: 2084-2094, 1991a.
36. Blair RW, Evans AR. Responses of medullary raphespinal neurons to coronary artery occlusion, epicardial bradykinin, and cardiac mechanical stimuli in cats. *J Neurophysiol* 66: 2095-2106, 1991b.
37. Blair RW, Weber RN, Foreman RD. Characteristics of primate spinothalamic tract neurons receiving viscerosomatic convergent inputs in T3-T5 segments. *J Neurophysiol* 46: 797-811, 1981.
38. Blair RW, Weber RN, Foreman RD. Responses of thoracic spinothalamic neurons to intracardiac injection of bradykinin in the monkey. *Cir Res* 51: 83-94, 1982.
39. Blair RW, Weber RN, Foreman RD. Responses of thoracic spinoreticular and spinothalamic cells to intracardiac bradykinin. *Am J Physiol* 246: H500-H507, 1984.
40. Blomqvist A, Ma W, Berkley KJ. Spinal input to the parabrachial nucleus in the cat. *Brain Res* 480: 29-36, 1989.
41. Boivie J. An anatomical reinvestigation of the termination of the spinothalamic tract in the monkey. *J Comp Neurol* 186: 343-370, 1979.
42. Bolser DC, Chandler MJ, Garrison DW, Foreman RD. Effects of intracardiac bradykinin and capsaicin on spinal and spinoreticular neurons. *Am J Physiol* 257: H1543-H1550, 1989.
43. Bonica JJ. *Management of Pain*. London: Lea & Febiger, pp. 133-179, 1990.
44. Bradesi S. Role of spinal cord glia in the central processing of peripheral pain perception. *Neurogastroenterol Motil* 22: 499-511, 2010.
45. Brennan TJ, Oh U-T, Girardot M-N, Ammons WS, Foreman RD. Inhibition of cardiopulmonary input to thoracic spinothalamic tract cells by stimulation of the subcoeruleus-parabrachial region in the primate. *J.Auton Nerv Sys* 18: 61-72, 1987.
46. Brook RA, Wahlqvist P, Kleinman NL, Wallander MA, Campbell SM, Smeeding JE. Cost of gastro-oesophageal reflux disease to the employer: A perspective from the United States. *Aliment Pharmacol Ther* 26: 889-898, 2007.
47. Brown AM, Malliani A. Spinal sympathetic reflexes initiated by coronary receptors. *J Physiol* 212: 685-705, 1971.
48. Burstein R. Somatosensory and visceral input to the hypothalamus limbic system. *Prog Brain Res* 107: 257-267, 1996.
49. Burton, H., Loewy, A.D. Descending projections from the marginal cell layer and other regions of the monkey spinal cord. *Brain Res* 116: 485-491, 1976.
50. Camilleri M, Saslow SB, Bharucha AE. Gastrointestinal sensation. Mechanisms and relation to functional gastrointestinal disorders. *Gastroenterol Clin North Am* 25: 247-258, 1996.
51. Cannon RO 3rd, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 61: 1338-1343, 1988.
52. Cannon, Watson RM, Rosing DR, Epstein SE. Angina caused by reduced vasodilator reserve of the small coronary arteries. *J Am Coll Cardiol* 1: 1359-1373, 1983.
53. Casati R, Lombardi F, Malliani A. Afferent sympathetic unmyelinated fibres with left ventricular endings in cats. *J Physiol* 292: 135-148, 1979.
54. Casey KL, Jones EG. Supraspinal mechanisms: An overview of ascending pathways: brainstem and thalamus. *Neurosci Res Prog Bull* 16: 103-118, 1978.
55. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* 389: 816-824, 1997.

56. Cechetto DF, Saper CB. Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. *J Comp Neurol* 262: 27-45, 1987.
57. Cechetto DF, Standaert DG, Saper CB. Spinal and trigeminal dorsal horn projections to the parabrachial nucleus in the rat. *J Comp Neurol* 240: 153-160, 1985.
58. Cervero F. Somatic and visceral inputs to the thoracic spinal cord of the cat: Effects of noxious stimulation of the biliary system. *J Physiol (Lond)* 337: 51-67, 1983.
59. Cervero F. Sensory innervation of the viscera: Peripheral basis of visceral pain. *Physiol Rev* 74: 95-138, 1994.
60. Cervero F. Visceral pain: Mechanisms of peripheral and central sensitization. *Ann Med* 27: 235-239, 1995.
61. Cervero F, Connell LA. Distribution of somatic and visceral primary afferent fibres within the thoracic spinal cord of the cat. *J Comp Neurol* 230: 88-98, 1984.
62. Cervero F, Janig W. Visceral nociceptors: A new world order. *Trends Neurosci* 15: 374-378, 1992.
63. Chandler MJ, Hobbs ST, Bolser DC, Foreman RD. Effects of vagal afferent stimulation on cervical spinothalamic tract neurons in monkeys. *Pain* 44: 81-87, 1991.
64. Chandler MJ, Zhang J, Foreman RD. Vagal, sympathetic and somatic sensory inputs to upper cervical (C1-C3) spinothalamic tract neurons in monkeys. *J Neurophysiol* 76: 2555-2567, 1996.
65. Chandler MJ, Zhang J, Qin C, Foreman RD. Spinal inhibitory effects of cardiopulmonary afferent inputs in monkeys: Neuronal processing in high cervical segments. *J Neurophysiol* 87: 1290-1302, 2002.
66. Chandler MJ, Zhang J, Qin C, Yuan Y, Foreman RD. Intrapericardiac injections of algogenic chemicals excite primate C1-C2 spinothalamic tract neurons. *Am J Physiol Regul Integr Comp Physiol* 279: R560-R568, 2000.
67. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Cardioesophageal reflex: A mechanism for "linked angina" in patients with angiographically proven coronary artery disease. *J Am Coll Cardiol* 27: 1621-1628, 1996.
68. Chauhan A, Petch MC, Schofield PM. Effect of oesophageal acid instillation on coronary blood flow. *Lancet* 341: 1309-1310, 1993.
69. Ciuffo AA, Ouyang P, Becker LC, Levin L, Weisfeldt ML. Reduction of sympathetic inotropic response after ischemia in dogs. Contributor to stunned myocardium. *J Clin Invest* 75: 1504-1509, 1985.
70. Cohn PF. Silent myocardial ischemia. *Ann Intern Med* 109: 312-317, 1988.
71. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. *Circulation* 108: 1263-1277, 2003.
72. Coleridge HM, Coleridge JCG. Cardiovascular afferents involved in regulation of peripheral vessels. *Annu Rev Physiol* 42: 413-427, 1980.
73. Coleridge HM, Coleridge JCG, Kidd C. Cardiac receptors in the dog with particular reference to two types of endings in the ventricular wall. *Physiol (Lond)* 174: 323-339, 1964.
74. Coleridge JCG, Hemingway A, Holmes RL, Linden RJ. The location of atrial receptors in the dog: A physiological and histological study. *Physiol (Lond)* 136: 174-197, 1957.
75. Covey WC, Ignatowski TA, Renauld AE, Knight PR, Nader ND, Spengler RN. Expression of neuron-associated tumor necrosis factor alpha in the brain is increased during persistent pain. *Reg Anesth* 27: 357-366, 2002.
76. Crea F, Biasucci LM, Buffon A, Liuzzo G, Monaco C, Caligiuri G, Kol A, Sperti G, Cianflone D, Maseri A. Role of inflammation in the pathogenesis of unstable coronary artery disease. *Am J Cardiol* 80(5A): 10E-16E, 1997.
77. Csendes A, Sepulveda A. Intraluminal gallbladder pressure measurements in patients with chronic or acute cholecystites. *Am J Surg* 13: 383-385, 1980.
78. Cullen M L, Reese HL. Myocardial circulatory changes measured by clearance of Na24-effect of common duct distension on myocardial circulation. *J Appl Physiol* 5: 281-284, 1952.
79. Cunha FQ, Poole S, Lorenzetti BB, Ferreira SH. The pivotal role of tumour necrosis factor alpha in the development of inflammatory hyperalgesia. *Br J Pharmacol* 107: 660-664, 1992.
80. Dean BB, Crawley JA, Schmitt CM, Wong J, Ofman JJ. The burden of illness of gastro-oesophageal reflux disease: Impact on work productivity. *Aliment Pharmacol Ther* 17: 1309-1317, 2003.
81. De Biasi S, Rustioni A. Glutamate and substance P coexist in primary afferent terminals in the superficial laminae of spinal cord. *Proc Natl Acad Sci USA* 85: 7820-7824, 1988.
82. Deedwania PC, Carbajal EV. Prevalence and patterns of silent myocardial ischemia during daily life in stable angina patients receiving conventional antianginal drug therapy. *Am J Cardiol* 65: 1090-1096, 1990.
83. De Leo JA, Tawfik VL, LaCroix-Fralish ML. The tetrapartite synapse: Path to CNS sensitization and chronic pain. *Pain* 122: 17-21, 2006.
84. Dejongste MJ, Hautvast RW, Ruiters MH, Ter Horst GJ. Spinal cord stimulation and the induction of c-fos and heat shock protein 72 in the central nervous system of rats. *Neuromodulation* 1: 73-84, 1998.
85. DeVon, HA, Zerwic, JJ. The symptoms of unstable angina: Do women and men differ? *Nurs Res* 52, 108-118, 2003.
86. Dobrzycki S, Baniukiewicz A, Korecki J, Bachorzewska-Gajewska H, Prokopczuk P, Musial WJ, Kaminski KA, Dabrowski A. Does gastroesophageal reflux provoke the myocardial ischemia in patients with CAD? *Int J Cardiol* 104: 67-72, 2005.
87. Donald DE, Shepherd JT. Reflexes from the heart and lungs; Physiological curiosities or important regulatory mechanisms. *Cardiavasc Res* 12: 449-469, 1978.
88. Douglas, PS., Ginsburg, GS. The evaluation of chest pain in women. *N Engl J Med* 334: 1311-1315, 1996.
89. Downman CBB. Skeletal muscle reflexes of splanchnic and intercostal nerve origin in acute and decerebrate cats. *J Neurophysiol* 18: 217-235, 1955.
90. Downman CBB. The distribution of splanchnic afferents in the spinal cord of the cat. *J Physiol (Lond)* 137: 66-79, 1957.
91. Drewes AM, Schipper KP, Dimcevski G, Petersen P, Andersen OK, Gregersen H, Arendt-Nielsen L. Multimodal assessment of pain in the esophagus: A new experimental model. *Am J Physiol Gastrointest Liver Physiol* 283: G95-G103, 2002.
92. Drewes AM, Schipper KP, Dimcevski G, Petersen P, Andersen OK, Gregersen H, Arendt-Nielsen L. Multi-modal induction and assessment of allodynia and hyperalgesia in the human oesophagus. *Eur J Pain* 7: 539-49, 2003.
93. Droste C, Greenlee MW, Roskamm H. A defective angina pectoris pain warning system: Experimental findings of ischemic and electrical pain test. *Pain* 26: 199-209, 1986.
94. Droste C, Roskamm H. Experimental pain measurement in patients with asymptomatic myocardial ischemia. *Am Coll Cardiol* 1: 940-945, 1983.
95. Duggan AW. Release of neuropeptide in the spinal cord. In: Nyberg F, Sharma HS, Wiesenfeld-Hallin Z, editors. *Neuropeptides in the Spinal Cord Progress in Brain Research*. New York: Elsevier, pp. 197-223, 1995.
96. Duggan AW, Hendry IA, Green LJ, Morton CR, and Zhao ZQ. Cutaneous stimuli releasing immunoreactive substance P in the dorsal horn of the cat. *Brain Res* 451: 261-273, 1988.
97. Eriksson B, Svedenhag J, Martinsson A, Sylvén C. Effect of epinephrine infusion on chest pain in syndrome X in the absence of signs of myocardial ischaemia. *Am J Cardiol* 75: 241-245, 1995.
98. Euchner-Wamser I, Meller ST, Gebhart GF. A model of cardiac nociception in chronically instrumented rats: Behavioral and electrophysiological effects of pericardial administration of algogenic substances. *Pain* 58: 117-128, 1994.
99. Falcone C, Sconocchia R, Guasti L, Codega S, Monetrnartini C, Specchia G. Dental pain threshold and angina pectoris in patients with coronary artery disease. *Am Coll Cardiol* 12: 348-352, 1988.
100. Farrokhi F, Vaezi MF. Extra-esophageal manifestations of gastroesophageal reflux. *Oral Dis* 13: 349-359, 2007.
101. Felder RB, Thames MD. Interaction between cardiac receptors and sinoaortic baroreceptors in the control of efferent cardiac sympathetic nerve activity during myocardial ischemia in dogs. *Circ Res* 45: 728-736, 1979.
102. Feng Y, Cui M, Al-Chaer ED, Willis WD. Epigastric antinociception by cervical dorsal column lesions in rats. *Anesthesiology* 89: 411-420, 1998.
103. Ferreira SH. Prostaglandins, aspirin-like drugs and analgesia. *Nat New Biol* 240: 200-203, 1972.
104. Festi D, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, Colecchia A. Incidence of gallstone disease in Italy: Results from a multicenter, population-based Italian study (the MICOL project). *World J Gastroenterol* 14: 5282-5289, 2008.
105. Fields HL, Basbaum AI, Clanton CH, Anderson SD. Nucleus raphe magnus inhibition of spinal cord dorsal horn neurons. *Brain Res* 126: 441-453, 1977.
106. Flores NA, Sheridan DJ. The pathophysiological role of platelets during myocardial ischaemia. *Cardiovasc Res* 28: 295-302, 1994.
107. Foreman RD. Mechanisms of cardiac pain. *Annu Rev Physiol* 61: 143-167, 1999.
108. Foreman RD, Applebaum AE, Beall JE, Trevino DL, Willis WD. Responses of primate spinothalamic tract neurons to electrical stimulation of hindlimb peripheral nerves. *J Neurophysiol* 38: 132-145, 1975.
109. Foreman RD, Blair RW, Weber RN. Viscerosomatic convergence onto T2-T4 spinoreticular, spinoreticular-spinothalamic, and spinothalamic tract neurons in the cat. *Exp Neurol* 85: 597-619, 1984.
110. Foreman RD, Qin C. Neuromodulation of cardiac pain and cerebral vasculature: neural mechanisms. *Cleve Clin J Med* 76(Suppl 2): S75-S79, 2009.
111. Franco-Cereceda A, Liska J. Potential of calcitonin gene-related peptide in coronary heart disease. *Pharmacology* 60: 1-8, 2000.

112. Francis J, Zhang Z-H, Weiss RM, Felder RB. Neural regulation of the proinflammatory cytokine response to acute myocardial infarction. *Am J Physiol Heart Circ Physiol* 287: H791-H797, 2004.
113. Frangogiannis N, Lindsey ML, Michael LH, Youker KA, Bressler RB, Mendoza LH, Spengler RN, Smith CW, Entman ML. Resident cardiac mast cells degranulate and release preformed TNF-a, initiating the cytokine cascade in experimental canaine myocardial ischemia/reperfusion. *Circulation* 98: 699-710, 1998.
114. Frank L, Kleinman L, Ganoczy D, McQuaid K, Sloan S, Eggleston A, Tougas G, Farup C. Upper gastrointestinal symptoms in North America: Prevalence and relationship to healthcare utilization and quality of life. *Dig Dis Sci* 45: 809-818, 2000.
115. Frot M, Mauguiere F. Dual representation of pain in the operculoinsular cortex in humans. *Brain* 126: 438-450, 2003.
116. Fu L-W, Longhurst JC. Interactions between histamine and bradykinin in stimulation of ischaemically sensitive cardiac afferents in felines. *J Physiol (Lond)* 565: 1007-1017, 2005.
117. Fu L-W and Longhurst JC. Regulation of cardiac afferent excitability in ischemia. Sensory serves. In: Canning BJ, Spina D, editors. *Handbook of Experimental Pharmacology*. Springer-Verlag Berlin Heidelberg, Vol. 194; pp. 185-225, 2009.
118. Fu L-W, Longhurst JC. Bradykinin and thromboxane A2 reciprocally interact to synergistically stimulate cardiac spinal afferents during myocardial ischemia. *Am J Physiol Heart Circ Physiol* 298: H235-H244, 2010.
119. Garrison DW, Chandler MJ, Foreman RD. Viscerosomatic convergence onto feline spinal neurons from esophagus, heart and somatic fields: Effects of inflammation. *Pain* 49: 373-382, 1992.
120. Gaspardone A, Crea F, Tomai F, Iamele M, Crossman DC, Pappagallo M, Versaci F, Chiariello L, Gioffrè PA. Substance P potentiates the algogenic effects of intraarterial infusion of adenosine. *J Am Coll Cardiol* 24: 477-482, 1994.
121. Gebhart GF. Pathobiology of visceral pain: molecular mechanisms and therapeutic implications IV. Visceral afferent contributions to the pathobiology of visceral pain. *Am J Physiol Gastrointest Liver Physiol* 278: G834-G838, 2000.
122. Gegelashvili G, Schousboe A. High afinity glutamate transporters: Regulation of expression and activity. *Mol Pharmacol* 52: 6-15, 1997.
123. Geppetti P, Maggi CA, Perretti F, Frilli S, Manzini S. Simultaneous release by bradykinin of substance P-and calcitonin gene-related peptide immunoreactivities from capsaicin-sensitive structures in guinea-pig heart. *Br J Pharmacol* 94: 288-290, 1988.
124. Gerhart KD, Wilcox TK, Chung JM, Willis WD. Inhibition of nociceptive and nonnociceptive responses of primate spinothalamic cells by stimulation in medial brain stem. *J Neurophysiol* 45: 121-136, 1981.
125. Ghione S, Rosa C, Mezzasalma L, Panattoni E. Arterial hypertension is associated with hypalgesia in humans. *Hypertension* 12: 491-497, 1988.
126. Giamberardino MA, Costantini R, Affaitati G, Fabrizio A, Lapenna D, Tafuri E, Mezzetti A. Viscero-visceral hyperalgesia: Characterization in different clinical models. *Pain* 151: 307-322, 2010.
127. Girardot M-N, Brennan TJ, Ammons WS, Foreman RD. Effects of stimulating the subcoeruleus-parabrachial region on the non-noxious and noxious responses of T2-T4 spinothalamic tract neurons in the primate. *Brain Res* 409: 19-30, 1987.
128. Glazier JJ, Chierchia S, Brown MJ, Maseri A. Importance of generalized defective perception of painful stimuli as a cause of silent myocardial ischemia in chronic stable angina pectoris. *Am J Cardiol* 58: 667-672, 1986.
129. Goodman-Keiser MD, Qin C, Thompson AM, Foreman RD. Upper thoracic postsynaptic dorsal column neurons conduct cardiac mechanoreceptive information, but not cardiac chemical nociception in rats. *Brain Res* 1366: 71-84, 2010.
130. Greenwood-Van Meerveld B, Gibson M, Gunter W, Shepard J, Foreman R, Myers D. Stereotaxic delivery of corticosterone to the amygdala modulates colonic sensitivity in rats. *Brain Res* 893: 135-142, 2001.
131. Gunter WD, Shepard JD, Foreman RD, Myers DA, Greenwood-Van Meerveld B. Evidence for visceral hypersensitivity in high anxiety rats. *Physiol Behav* 69: 379-382, 2000.
132. Guo Z, Niu Y-L, Zhang J-W, Yao T-P. Coronary artery occlusion alters expression of substance P and its mRNA in spinal dorsal horn in rats. *Neuroscience* 145: 669-675, 2007.
133. Gutterman DD. Silent myocardial ischemia. *Circ J* 73: 785-97, 2009.
134. Gutterman DD, Morgan DA, Miller FJ. Effect of brief myocardial ischemia on sympathetic coronary vasoconstriction. *Circ Res* 71: 960-969, 1992.
135. Habler HJ, Janig W, Koltzenburg M. Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat. *J Physiol (Lond)* 425: 545-562, 1990.
136. Hammond DL, Proudfit HK. Effects of locus coeruleus lesions on morphine-induced antinociception. *Brain Res* 188: 79-91, 1980.
137. Hampton AG, Beckwith JR, Wood JE. The relationship between heart disease and gallbladder disease. *Ann Intern Med* 50: 1135-1148, 1959.
138. Hancock MB, Fougerousse CL. Spinal projections from the nucleus locus coeruleus and nucleus subcoeruleus in the cat and monkey as demonstrated by the retrograde transport of horseradish peroxidase. *Brain Res Bull* 1: 229-234, 1976.
139. Harrison TR & Reeves TJ. Patterns and causes of chest pain. In: Harrison TR, Reeves TJ, editor. *Principles and Problems of Ischemic Heart Disease*. Chicago: YearBook Medical, pp. 197-204, 1968.
140. Healy B. The Yentl syndrome. *N Engl J Med* 325: 274-276, 1991.
141. Hekmatpanah J. Organization of tactile dermatomes, C1 in cat. *J. Neurophysiol* 264: 582-586, 1961.
142. Herkenham M. Laminar organization of thalamic projections to the rat neocortex. *Science* 207: 532-535, 1980.
143. Herlitz J, Bång A, Karlson BW, Hartford M. Is there a gender difference in aetiology of chest pain and symptoms associated with acute myocardial infarction? *Eur J Emerg Med* 6: 311-315, 1999.
144. Hewson EG, Dalton CB, Hackshaw BT, Wu WC, Richter JE. The prevalence of abnormal esophageal test results in patients with cardiovascular disease and unexplained chest pain. *Arch Intern Med* 150: 965-969, 1990.
145. Hirsh P, Hillis L, Campbell W, Firth B, Willerson J. Release of prostaglandins and thromboxane into the coronary circulation in patients with ischemic heart disease. *N Engl J Med* 304: 685-691, 1981.
146. Hirshberg RM, Al-Chaer ED, Lawand NB, Westlund KN, Willis WD. Is there a pathway in the posterior funiculus that signals visceral pain? *Pain* 67: 291-305, 1996.
147. Hobbs SF, Chandler MJ, Bolser DC, Foreman RD. Segmental organization of visceral and somatic input onto C3-T6 spinothalamic tract cells of the monkey. *J Neurophysiol* 68: 1575-1588, 1992.
148. Hobbs SF, Oh UT, Chandler MJ, Foreman RD. Cardiac and abdominal vagal afferent inhibition of primate T9-S1 spinothalamic cells. *Am J Physiol* 257: R889-R895, 1989.
149. Hobson AR, Khan RW, Sarkar S, Furlong PL, Aziz Q. Development of esophageal hypersensitivity following experimental duodenal acidification. *Am J Gastroenterol* 99: 813-820, 2004.
150. Hodge GB, Messer AL, Hill H. Effect of distension of the biliary tract on the electrocardiogram. *Arch Surg* 55: 710-722, 1947.
151. Hökfelt T, Zhang X, Weisenfeld-Hallin Z. Messenger plasticity in primary sensory neurons following axotomy and its functional implications. *Trends Neuro Sci* 17: 22-30, 1994.
152. Holzer P. Capsaicin: Cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacol Rev* 43: 143-201, 1991.
153. Honoré P, Kamp EH, Rogers SD, Gebhart GF, Mantyh PW. Activation of lamina I spinal cord neurons that express the substance P receptor in visceral nociception and hyperalgesia. *J Pain* 3: 3-11, 2002.
154. Hopkins DA, Armour JA. Ganglionic distribution of afferent neurons innervating the canine heart and cardiopulmonary nerves. *J Auton Nerv Syst* 26: 213-222, 1989.
155. Hoover DB, Chang Y, Hancock JC, Zhang L. Actions of tachykinins within the heart and their relevance to cardiovascular disease. *Jpn J Pharmacol* 84: 367-373, 2000.
156. Hori T, Oka T, Hosoi M, Aou S. Pain modulatory actions of cytokines and prostaglandin E2 in the brain. *Ann NY Acad Sci* 840: 269-281, 1998.
157. Horie H, Yokota T. Responses of nociceptive VPL neurons to intracardiac injection of bradykinin in the cat. *Brain Res* 516: 161-164, 1990.
158. Houghton AK, Kadura S, Westlund KN. Dorsal column lesions reverse the reduction of home cage activity in rats with pancreatitis. *NeuroReport* 8: 3795-3800, 1997.
159. Hu WH, Martin CJ, Talley NJ. Intraesophageal acid perfusion sensitizes the esophagus to mechanical distension: A Barostat study. *Am J Gastroenterol* 95: 2189-2194, 2000.
160. Hu P, McLachlan EM. Long-term changes in the distribution of galanin in dorsal root ganglia after sciatic or spinal nerve transection in rats. *Neuroscience* 103: 1059-1071, 2001.
161. Hu P, McLachlan EM. Macrophage and lymphocyte invation of dorsal root ganglia after peripheral nerve lesions in the rat. *Neuroscience* 112: 23-38, 2002.
162. Hua F, Ardell JL, Williams CA. Left vagal stimulation induces dynorphin release and suppresses substance P release from the rat thoracic spinal cord during cardiac ischemia. *Am J Physiol Regul Integr Comp Physiol* 287: R1468-1477, 2004.
163. Hua F, Ricketts BA, Reifsteck A, Ardell JL, Williams CA. Myocardial ischemia induces the release of substance P from cardiac afferent neurons in rat thoracic spinal cord. *Am J Physiol Heart Circ Physiol* 286: H1654-H1664, 2004.
164. Humbertson A, Zimmermann E, Leedy M. A chronological study of mitotic activity in satellite cell hyperplasia associated with chromatolytic neurons. *Z Zellforsch* 100: 507-515, 1969.
165. Ignatowski TA, Covey WC, Knight PR, Severin CM, Nickola TJ, Spengler RN. Brain-derived TNFalpha mediates neuropathic pain. *Brain Res* 841: 70-77, 1999.

166. Janig W. (ed.). *The Integrative Action of the Autonomic Nervous System: Neurobiology of Homeostasis*. Cambridge: Cambridge University Press. pp. 65-85, 2006.
167. Janig W. Visceral pain–still an enigma? *Pain* 151: 239-240, 2010.
168. Jaspersen D. Extra-esophageal disorders in gastroesophageal reflux disease. *Dig Dis* 22: 115-119, 2004.
169. Ji R-R, Berta T, Nedergaard M. Glia and pain: Is chronic pain a gliopathy? *Pain* 154: S10-S28, 2013.
170. Johnston IN, Milligan ED, Wieseler-Frank J, Frank MG, Zapata V, Campisi J, Langer S, Martin D, Green P, Fleshner M, Leinwand L, Maier SF, Watkins LR. A role for proinflammatory cytokines and fractalkine in analgesia, tolerance, and subsequent pain facilitation induced by chronic intrathecal morphine. *J Neurosci* 24: 7353-7365, 2004.
171. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 413: 203-210, 2001.
172. Junger H, Sorkin LS. Nociceptive and inflammatory effects of subcutaneous TNF alpha. *Pain* 85: 145-151, 2000.
173. Karai L, Brown DC, Mannes AJ, Connelly ST, Brown J, Gandal M, Wellisch OM, Neubert JK, Olah Z, and Iadarola MJ. Deletion of vanilloid receptor 1-expressing primary afferent neurons for pain control. *J Clin Invest* 113: 1344-1352, 2004.
174. Katayama Y, Watkins LR, Becker DP, Hayes, RL. Non-opiate analgesia induced by carbacol microinjection into the pontine parabrachial region of the cat. *Brain Res* 296: 262-283, 1984.
175. Kaufman MP, Baker DG, Coleridge HM, ColeridgeJC. Stimulation by bradykinin of afferent vagal C-fibers with chemosensitive endings in the heart and aorta of the dog. *Circ Res* 46: 476-484, 1980.
176. Kellgren JH. Observations on referred pain arising from muscle. *Clin Sci* 3: 175-190, 1937-38.
177. Kellgren JH. Somatic simulating visceral pain. *Clin Sci* 4: 303-309, 1940.
178. Kezdi P, Kordenat RK, Misra SN. Reflex inhibitory effects of vagal afferents in experimental myocardial infarction. *Am J Cardiol* 33: 853-860, 1974.
179. Khabarova AY. *The Afferent Innervation of the Heart*. New York: Heart Consultants Bureau, 1961.
180. Khasabov SG, Rogers SD, Ghilardi JR, Peters CM, Mantyh PW, Simone DA. Spinal neurons that possess the substance P receptor are required for the development of central sensitization. *J Neurosci* 22: 9086-9098, 2002.
181. Kimura E, Hashimoto K, Furukawa S, Hayakawa H. Changes in bradykinin level in coronary sinus blood after the experimental occlusion of a coronary artery. *Am Heart J* 85: 635-647, 1973.
182. Kohchi K, Takebayashi S, Hiroki T, Nobuyoshi M. Significance of adventitial inflammation of the coronary artery in patients with unstable angina: Results at autopsy. *Circulation* 71: 709-716, 1985.
183. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: The concept of allergic angina. *Br J Clin Pract* 45: 121-127, 1991.
184. Kreiner M, Okeson JP. Toothache of cardiac origin. *J Orofac Pain* 13: 201-207, 1999.
185. Kreiner M, Okeson JP, Michelis V, Lujambio M, Isberg A. Craniofacial pain as the sole symptom of cardiac ischemia: A prospective multicenter study. *J Am Dent Assoc* 138: 174-179, 2007.
186. Kuo DC, Oravitz JJ, DeGroat WC. Tracing of afferent and efferent pathways in the left inferior cardiac nerve of the cat using retrograde and transganglionic transport of horseradish peroxidase. *Brain Res* 321: 111-118, 1984.
187. Lanza GA. Cardiac syndrome X: A critical overview and future perspectives. *Heart* 93: 159-166, 2007.
188. Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neural plasticity. *J Pain* 10: 895-926, 2009.
189. Lehre KP, Danbolt NC. The number of glutamate transporter subtype molecules at glutamatergic synapses: Chemical and stereological quantification in young adult rat brain. *J Neurosci* 18: 8751-8757, 1998.
190. Lenz FA, Dougherty PM, Traill TA. Thalamic mechanisms of chest pain in the absence of cardiac pathology. *Heart* 75: 429-430, 1996.
191. Lewis T. *Pain*. New York: Macmillan, 1942.
192. Levante A, Lamour Y, Guilbaud G, Besson JM. Spinothalamic cell activity in the monkey during intense nociceptive stimulation: Intra-arterial injection of bradykinin into the limbs. *Brain Res* 88: 560-564, 1975.
193. Linderoth B, Brodin E. Tachykinin release from rat spinal cord in vitro and in vivo in response to various stimuli. *Regul Pept* 21: 129-140, 1988.
194. Lindgren I, Olivecrona H. Surgical treatment of angina pectoris. *J Neurosurg* 4: 19-39, 1947.
195. Little JM, Qin C, Farber JP, Foreman RD. Spinal cord processing of cardiac nociception: Are there sex differences between male and proestrous female rats? *Brain Res* 1413: 24-31, 2011.
196. Liuzzo JP, Ambrose JA. Chest pain from gastroesophageal reflux disease in patients with coronary artery disease. *Cardiol Rev* 13: 167-173, 2005.
197. Lombardi F, Casalone C, Della Bella P, Malfatto G, Pagani M, Malliani A. Global versus regional myocardial ischaemia: Differences in cardiovascular and sympathetic responses in cats. *Cardiovasc Res* 18: 14-23, 1984.
198. Lombardi F, Della Bella P, Casati R, Malliani A. Effects of intracoronary administration of bradykinin on the impulse activity of afferent sympathetic unmyelinated fibers with left ventricular endings in the cat. *Circ Res* 48: 69-75, 1981.
199. Løvlien M, Schei B, Gjengedal E. Are there gender differences related to symptoms of acute myocardial infarction? A Norwegian perspective. *Prog Cardiovasc Nurs* 21: 14-19, 2006.
200. Lu X, Richardson PM. Responses of macrophages in rat dorsal root ganglia following peripheral nerve injury. *J. Neurocytol* 22: 334-341, 1993.
201. Lynn RB. Mechanisms of esophageal pain. *Am J Med* 92: 11S-19S, 1992.
202. Ma QP. Expression of capsaicin receptor (VR1) by myelinated primary afferent neurons in rats. *Neurosci Lett* 319: 87-90, 2002.
203. Maixner W, Randich A. Role of the right vagal nerve trunk in antinociception. *Brain Res* 298: 374-377, 1984.
204. Maixner W, Touw KB, Brody MJ, Gebhart GF, Long JP. Factors regulating the altered pain perception in the spontaneously hypertensive rat. *Brain Res* 237: 137-145, 1982.
205. Malfertheiner P, Hallerbäck B. Clinical manifestations and complications of gastroesophageal reflux disease (GERD). *Int J Clin Pract* 59: 346-355, 2005.
206. Malliani A. Cardiovascular and sympathetic afferent fibers. *Rev Physiol Biochem Pharmacol* 94: 11-74, 1982.
207. Maseri A, Crea F, Kaski JC, and Davies G. Mechanisms and significance of cardiac ischemic pain. *Prog Cardiovasc Dis* 35: 1-18, 1992.
208. Mason P. Contributions of the medullary raphe and ventromedial reticular region to pain modulation and other homeostatic functions. *Annu Rev Neurosci* 24: 737-777, 2001.
209. Matsushita, M., Ikeda, M., Hosoya. Y. The location of spinal neurons with long descending axons (long descending propriospinal tract neurons) in the cat: A study with horseradish peroxidase technique. *J Comp Neurol* 184: 63-80, 1979.
210. Mayer ML, Westbrook GL. The physiology of excitatory amino acids in the vertebrate central nervous system. *Prog Neurobiol* 28: 197-276, 1987.
211. McArthur SW, Wakefield H. Observations on the human electrocardiogram during experimental distension of the gallbladder. *J Lab Clin Med* 30: 349-351, 1945.
212. McMahon SB, Cafferty WB, Marchand F. Immune and glial cell factors as pain mediators and modulators. *Exp Neurol* 192: 444-462, 2005.
213. McMahon SB, Wall PD. Electrophysiological mapping of brainstem projections of spinal cord lamina I cells in the rat. *Brain Res.* 333: 19-26, 1985.
214. McNeill DL, Chandler MJ, Fu QG, Foreman RD. Projection of nodose ganglion cells to the upper cervical spinal cord in the rat. *Brain Res Bull* 27: 151-155, 1991.
215. Mehler WR, Feferman ME, Nauta WJH. Ascending axon degeneration following anterolateral cordotomy. An experimental study in the monkey. *Brain* 83: 718-751, 1960.
216. Mellow MH, Simpson AG, Watt L, Schoolmeester L, Haye OL. Esophageal acid perfusion in coronary artery disease. Induction of myocardial ischemia. *Gastroenterology* 85: 306-312, 1983.
217. Melzack R, Casey KL. Sensory, motivational and central control determinants of pain. In: Kenshalo DR, editor. *The Skin Senses*. Springfield, IL: Thomas, pp. 423-443, 1968.
218. Melzack R, Wall PD. *The Challenge of Pain*. New York: Basic Books, 1982.
219. Menétrey D, Basbaum AI. Spinal and trigeminal projections to the nucleus of the solitary tract: A possible substrate for somatovisceral and viscerovisceral reflex activation. *J Comp Neurol* 255: 439-450, 1987.
220. Menétrey D, De Pommery J. Origins of spinal ascending pathways that reach central areas involved in visceroception and visceronociception in the rat. *Eur J Neurosci* 3: 249-259, 1991.
221. Methot J, Hamelin BA, Bogaty P, Arsenault M, Plante S, Poirier P. Does hormonal status influence the clinical presentation of acute coronary syndromes in women? *J Women's Health (Larchmt)* 13: 695-702, 2004.
222. Meyer RA, Campbell JN. A novel electrophysiological technique for locating cutaneous nociceptive and chemospecific receptors. *Brain Res* 441: 81-86, 1988.
223. Michaelis M, Habler HJ, Jaenig W. Silent afferents: A separate class of primary afferents? *Clin Exp Pharmacol Physiol* 23: 99-105, 1996.
224. Miller HR. The interrelationship of disease of the coronary arteries and gallbladder. *Am Heart J* 24: 579-587, 1942.
225. Miller, KE, Douglas, VD, Richards, AB, Chandler, MJ, Foreman, RD. Propriospinal neurons in the C1-C2 spinal segments project to the L5-S1 segments of the rat spinal cord. *Brain Res Bull* 47: 43-47, 1998.

226. Miller MR, Kasahara M. Studies on the nerve endings in the heart. *Am J Anat* 115: 217-233, 1964.
227. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. *Nat Rev Neurosci* 10: 23-36, 2009.
228. Minisi AJ, Thames MD. Distribution of left ventricular sympathetic afferents demonstrated by reflex responses to transmural myocardial ischemia and to intracoronary and epicardial bradykinin. *Circulation* 87: 240-246, 1993.
229. Miyazaki T, Zipes DP. Presynaptic modulation of efferent sympathetic and vagal neurotransmission in the canine heart by hypoxia, high K+, low pH, and adenosine. Possible relevance to ischemia-induced denervation. *Circ Res* 66: 289-301, 1990.
230. Mtui EP, Anwar M, Gomez R, Reis DJ, Ruggiero DA. Projections from the nucleus tractus solitarii to the spinal cord. *J Comp Neurol* 337: 231-252, 1993.
231. Muers MF, Sleight P. Action potentials from ventricular mechanoreceptors stimulated by occlusion of the coronary sinus in the dog. *J Physiol (Lond)* 221: 283-309, 1972.
232. Murphy PG, Grondin J, Altares M, Richardson PM. Induction of interleukin-6 in axotomized sensory neurons. *J Neurosci* 15: 5130-5138, 1995.
233. Myers DE. Vagus nerve pain referred to the craniofacial region. A case report and literature review with implications for referred cardiac pain. *Br Dent J* 204: 187-189, 2008.
234. Nauta HJ, Hewitt E, Westlund KN, Willis Jr WD. Surgical interruption of a midline dorsal column visceral pain pathway. Case report and review of the literature. *J Neurosurg* 86: 538-542, 1997.
235. Nerdrum T, Baker DG, Coleridge HM, Coleridge JCG. Interaction of bradykinin and prostaglandin E1 on cardiac pressor reflex and sympathetic afferents. *Am J Physiol* 250: R815-R822, 1986.
236. Ness TJ, Metcalf AM, Gebhart GF. A psychophysiological study in humans using phasic colonic distention as a noxious visceral stimulus. *Pain* 43: 377-386, 1990.
237. Nihoyannopoulos P, Kaski JC, Crake T, Maseri A. Absence of myocardial dysfunction during pacing stress in patients with syndrome X. *J Am Coll Cardiol* 18: 1463-1470, 1991.
238. Niu Y-L, Guo Z, Zhou R-H. Up-regulation of TNF-a in neurons of dorsal root ganglia and spinal cord during coronary artery occlusion in rats. *Cytokine* 47: 23-29, 2009.
239. Nowicki D, Szulczyk P. Longitudinal distribution of negative cord dorsum potentials following stimulation of afferent fibres in the left inferior cardiac nerve. *J Auton Nerv Syst* 17: 185-197, 1986.
240. Oberg B, Thoren P. Circulatory responses to stimulation of medullated and non-medullated afferents in the cardiac nerve of the cat. *Acta Physiol Scand* 87: 121-132, 1972.
241. Opherk D, Zebe H, Weihe E, Mall G, Durr C, Gravert B. Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. *Circulation* 63: 817-825, 1981.
242. Ordway GA, Longhurst JC. Cardiovascular reflexes arising from the gallbladder of the cat: Effects of capsaicin, bradykinin, and distension. *Circ Res* 52: 26-35, 1983.
243. Ostrowsky K, Magnin M, Ryvlin P. Representation of pain and somatic sensation in the human insula: A study of responses to direct electrical cortical stimulation. *Cereb Cortex* 12: 376-385, 2002.
244. Paintal AS. Vagal sensory receptors and their reflex effects. *Physiol Rev* 53: 159-227, 1973.
245. Pal P, Koley J, Bhattacharyya S, Gupta JS, Koley B. Cardiac nociceptors and ischemia: Role of sympathetic afferents in cat. *Jpn J Physiol* 39: 131-144, 1989.
246. Palecek J, Paleckova V, Willis WD. Fos expression in spinothalamic and postsynaptic dorsal column neurons following noxious visceral and cutaneous stimuli. *Pain* 104: 249-257, 2003.
247. Pan HL, Longhurst JC. Lack of a role of adenosine in activation of ischemically sensitive cardiac sympathetic afferents. *Am J Physiol HeartCirc Physiol* 269: H106-H113, 1995.
248. Pan HL, Longhurst JC. Ischaemia-sensitive sympathetic afferents innervating the gastrointestinal tract function as nociceptors in cats. *J Physiol (Lond)* 492: 841-850, 1996.
249. Pan HL, Longhurst JC, Eisenach JC, Chen SR. Role of protons in activation of cardiac sympathetic C-fibre afferents during ischaemia in cats. *J Physiol (Lond)* 518: 857-866, 1999.
250. Pan HL, Chen SR. Myocardial ischemia recruits mechanically insensitive cardiac sympathetic afferents in cats. *J Neurophysiol* 87: 660-668, 2002.
251. Pan HL, Chen SR. Sensing tissue ischemia: Another new function for capsaicin receptors? *Circulation* 110: 1826-1831, 2004.
252. Pan HL, Khan GM, Alloway KD, and Chen SR. Resiniferatoxin induces paradoxical changes in thermal and mechanical sensitivities in rats: Mechanism of action. *J Neurosci* 23: 2911-2919, 2003.
253. Panneton WM, Burton H. Projections from the paratrigeminal nucleus and the medullary and spinal dorsal horn to the peribrachial area in the cat. *Neuroscience* 15: 779-798, 1985.
254. Panza JA, Laurienzo JM, Curiel RV. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol* 29: 293-301, 1997.
255. Pasceri V, Lanza GA, Buffon A. Role of abnormal pain sensitivity and behavioural factors in determining chest pain in syndrome X. *J Am Coll Cardiol* 31: 62-66, 1998.
256. Patel H, Rosengren A, Ekman I. 2004. Symptoms in acute coronary syndromes: Does sex make a difference? *Am Heart J* 148: 27-33, 2004.
257. Pedersen F, Pieterson A, Madsen JK, Ballegaard S, Meyer C, Trojaborg W. Elevated pain threshold in patients with effort-induced angina pectoris and asymptomatic myocardial ischemia during exercise test. *Clin Cardiol* 12: 639-642, 1989.
258. Pedersen J, Reddy H, Funch-Jensen P, Arendt-Nielsen L, Gregersen H, Drewes AM. Differences between male and female responses to painful thermal and mechanical stimulation of the human esophagus. *Dig Dis Sci* 49: 1065-1074, 2004.
259. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci* 21: 9896-9903, 2001.
260. Price DD, Dubner R. Neurons that subserve the sensory-discriminative aspects of pain. *Pain* 3: 307-338, 1977.
261. Procacci P, Zoppi M. Heart pain. In: *Textook of Pain*. Edinburgh: Churchill Livingstone. pp. 410-419, 1989.
262. Qin C, Chandler MJ, Miller KE, Foreman RD. Responses and afferent pathways of superficial and deeper c(1)-c(2) spinal cells to intrapericardial algogenic chemicals in rats. *J Neurophysiol* 84: 1522-1532, 2001.
263. Qin C, Chandler MJ, Foreman RD. Esophagocardiac convergence onto thoracic spinal neurons: comparison of cervical and thoracic esophagus. *Brain Res* 1008: 193-197, 2004.
264. Qin C, Chandler MJ, Jou CJ, Foreman RD. Responses and afferent pathways of C1-C2 spinal neurons to cervical and thoracic esophageal stimulation in rats. *Neurophysiol* 91: 2227-2235, 2004.
265. Qin C, Chandler MJ, Miller KE, Foreman RD. Chemical activation of cardiac receptors affects activity of superficial and deeper T3-T4 spinal neurons in rats. *Brain Res* 959: 77-85, 2003.
266. Qin C, Farber JP, Foreman RD. Intraesophageal chemicals enhance responsiveness of upper thoracic spinal neurons to mechanical stimulation of esophagus in rats. *Am J Physiol Gastrointest Liver Physiol* 294: G708-G716, 2008.
267. Qin C, Farber JP, Miller KE, Foreman RD. Responses of thoracic spinal neurons to activation and desensitization of cardiac TRPV1-containing afferents in rats. *Am J Physiol Regul Integr Comp Physiol* 291: R1700-R1707, 2006.
268. Qin C, Foreman RD, Farber JP. Characterization of thoracic spinal neurons with noxious convergent inputs from heart and lower airways in rats. *Brain Res* 1141: 84-91, 2007.
269. Qin C, Greenwood-Van Meerveld B, Foreman RD. Spinal neuronal responses to urinary bladder stimulation in rats with corticosterone or aldosterone onto the amygdala. *J Neurophysiol* 90: 2180-2189, 2003.
270. Qin C, Greenwood-Van Meerveld B, Myers DA, Foreman RD. Corticosterone acts directly at the amygdala to alter spinal neuronal activity in response to colorectal distension. *J Neurophysiol* 89: 1343-1352, 2003.
271. Qin C, Kranenburg A, Foreman RD. Descending modulation of thoracic visceroreceptive transmission by C1-C2 spinal neurons. *Auton Neurosci* 114: 11-16, 2004.
272. Qin C, Malykhina AP, Thompson AM, Farber JP, Foreman RD. Cross-organ sensitization of thoracic spinal neurons receiving noxious cardiac input in rats with gastroesophageal reflux. *Am J Physiol Gastrointest Liver Physiol* 298: G934-G942, 2010.
273. Quigg M. Distribution of vagal afferent fibers of the guinea pig heart labeled by anterograde transport of conjugated horseradish peroxidase. *J Auton Nerv Syst* 36: 13-24, 1991.
274. Quigg M, Elfvin LG, Aldskogius H. Distribution of cardiac sympathetic afferent fibers in the guinea pig heart labeled by anterograde transport of wheat germ agglutinin-horseradish peroxidase. *J Auton Nerv Syst* 25: 107-118, 1988.
275. Randall WC, Hasson DM, Brady JV. Acute cardiovascular consequences of anterior descending coronary artery occlusion in unanesthetized monkey. *Proc Soc Exp Biol Med* 58: 135-140, 1978.
276. Randich A, Aicher SA. Medullary substrates mediating antinociception produced by electrical stimulation of the vagus. *Brain Res* 445: 68-76, 1988.
277. Randich A, Ren K, Gebhart GF. Electrical stimulation of cervical vagal afferents. II. Central relays for behavioral antinociception and arterial blood pressure decreases. *J Neurophysiol* 64: 1115-1124, 1990.
278. Randich A, Thurston CL. Antinociceptive states and hypertension. *J Cardiovasc Electrophysiol* 2(Suppl): S54-S58, 1991.
279. Ravdin IS, Fitzhugh T, Wolferth CC, Barbier EA, Ravdin GR. Relation of gallstone disease to angina pectoris. *Arch Surg* 70: 333-342, 1955.

280. Ravdin IS, Royster HP, Sanders GB. Reflexes originating in the common duct giving rise to pain simulating angina pectoris. *Ann Surg* 115: 1055-1062, 1942.
281. Recordati G, Lombardi F, Bishop VS, Malliani A. Response of type B atrial vagal receptors to changes in wall tension during atrial filling. *Circ Res* 36: 682-691, 1975.
282. Recordati G, Lombardi F, Bishop VS, Malliani A. Mechanical stimuli exciting type A atrial vagal receptors in the cat. *Circ Res* 38: 397-403, 1976.
283. Reddy H, Arendt-Nielsen L, Staahl C, Pedersen J, Funch-Jensen P, Gregersen H, Drewes AM. Gender differences in pain and biomechanical responses after acid sensitization of the human esophagus. *Dig Dis Sci* 50: 2050-2058, 2005.
284. Reis SE, Holubkov R, Lee JS. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol* 33: 1469-1475, 1999.
285. Ren K, Randich A, Gebhart GF. Vagal afferent modulation of spinal nociceptive transmission in the rat. *J Neurophysiol* 62: 401-415, 1989.
286. Ren K, Randich A, Gebhart GF. Modulation of spinal nociceptive transmission from nuclei tractus solitary: a relay for effects of vagal afferent stimulation. *J Neurophysiol* 63: 971-986, 1990a.
287. Ren K, Randich A, Gebhart GF. Electrical stimulation of cervical vagal afferents. I. Central relays for modulation of spinal nociceptive transmission. *J Neurophysiol* 64: 1098-1114, 1990b.
288. Ren K, Randich A, Gebhart GF. Effects of electrical stimulation of vagal afferents on spinothalamic tract cells in the rat. *Pain* 44: 311-319, 1991.
289. Richter JE. Beyond heartburn: extraesophageal manifestations of gastroesophageal reflux disease. *Am J Manag Care* 7(Suppl 1): S6-S9, 2001.
290. Rocco MB, Nabel EG, Campbell S, Goldman L, Barry J, Mead K, Selwyn AP. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* 78: 877-884, 1988.
291. Roesler H. Esophageal reflex origin of myocardial infarction. *Am J Med Sci* 240: 159-162, 1960.
292. Rosa C, Chione S, Panattoni E, Mezzasalma L, Giuliano G. Comparison of pain perception in normotensives and borderline hypertensives by means of a tooth pulp-stimulation test. *J Cardiovasc Pharmacal* 8(suppl5): S125-S127, 1986.
293. Rosano GM, Kaski JC, Arie S. Failure to demonstrate myocardial ischaemia in patients with angina and normal coronary arteries. Evaluation by continuous coronary sinus pH monitoring and lactate metabolism. *Eur Heart J* 17: 1175-1180, 1996.
294. Rosen SD. From heart to brain: The genesis and processing of cardiac pain. *Can J Cardiol* 28(2 Suppl): S7-S19, 2012.
295. Rosen SD, Paulesu E, Frith CD, Frackowiak RS, Davies GJ, Jones T, Camici PGl. Central nervous pathways mediating angina pectoris. *The Lancet* 344: 147-150, 1994.
296. Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RS, Frith CD, Jones T, Camici PG. Silent ischemia as a central problem: Regional brain activation compared in silent and painful myocardial ischemia. *Ann Int Med* 124: 939-949, 1996.
297. Rosen SD, Paulesu E, Wise RJS, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. *Heart* 87: 513-519, 2002.
298. Rosen SD, Uren NG, Kaski J-C, Tousoulis D, Davies GJ, Camici PG. Coronary vasodilator reserve, pain perception and gender in patients with syndrome X. *Circulation* 90: 50-60, 1994.
299. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, Kuncl RW, Kanai Y, Hediger MA, Wang Y, Schielke JP, Welty DF. Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. *Neuron* 16: 675-686, 1996.
300. Rozen JB, Schulkin J. From normal fear to pathological anxiety. *Psychol Rev* 105: 325-350, 1998.
301. Ruch TC. Pathophysiology of pain. In: Ruch TC, Patton HD, Woodbury JW, Towe AL, editors. *Neurophysiology*. Philadelphia: Saunders, pp. 350-368, 1961.
302. Saab CY, Wang J, Gu C, Garner KN, Al-Chaer ED. Microglia: A newly discovered role in visceral hypersensitivity? *Neuron Glia Biol* 2: 271-277, 2007.
303. Sadikot AF, Parent A, Francois C. The center median and parafascicular thalamic nuclei project respectively to the sensorimotor and associate limbic striatal territories in the squirrel monkey. *Brain Res* 510: 161-165, 1990.
304. Sakuma Y, Ohtori S, Miyagi M, Ishikawa T, Inoue G, Doya H, Koshi T, Ito T, Yamashita M, Yamauchi K, Suzuki M, Moriya H, and Takahashi K. Up-regulation of p55 TNF alpha-receptor in dorsal root ganglia neurons following lumbar facet joint injury in rats. *Eur Spine J* 16: 1273-1278, 2007.
305. Sampson JJ, Cheitlin MD. Pathophysiology and differential diagnosis of cardiac pain. *Prog Cardiovasc Dis* 13: 507-531, 1971.
306. Sandler RS, Everhart JE, Donowitz M. The burden of selected digestive diseases in the United States. *Gastroenterol* 122: 1500-1511, 2002.
307. Sarkar S, Aziz Q, Woolf CJ, Hobson AR, Thompson DG. Contribution of central sensitisation to the development of non-cardiac chest pain. *Lancet* 356: 1154-1159, 2000.
308. Sarkar S, Hobson AR, Furlong PL, Woolf CJ, Thompson DG, Aziz Q. Central neural mechanisms mediating human visceral hypersensitivity. *Am J Physiol Gastrointest Liver Physiol* 281: G1196-G1202, 2001.
309. Sarkar S, Thompson DG, Woolf CJ, Hobson AR, Millane T, Aziz Q. Patients with chest pain and occult gastroesophageal reflux demonstrate visceral pain hypersensitivity which may be partially responsive to acid suppression. *Am J Gastroenterol* 99: 1998-2006, 2004.
310. Sarkar S, Woolf CJ, Hobson AR, Thompson DG, Aziz Q. Perceptual wind-up in the human oesophagus is enhanced by central sensitisation. *Gut* 55: 920-925, 2006.
311. Schaible HG, Jarrot B, Hope PJ, and Duggan AW. Release of immunoreactive substance P in the spinal cord during development of acute arthritis in the knee joint of the cat: A study with antibody microprobes. *Brain Res* 529: 214-223, 1990.
312. Schaible HG, Schmidt RF. Time course of mechanosensitivity changes in articular afferents during a developing experimental arthritis. *J Neurophysiol* 60: 2180-2195, 1988.
313. Schang SJ, Pepine CJ. Transient asymptomatic S-T segment depression during daily activity. *Am J Cardiol* 39: 396-402, 1977.
314. Schofield PM, Whorwell PJ, Brooks NH, Bennett DH, Jones PE. Oesophageal function in patients with angina pectoris: A comparison of patients with normal coronary angiograms and patients with coronary artery disease. *Digestion* 42: 70-78, 1989.
315. Schultz HD, Ustinova EE. Cardiac vagal afferent stimulation by free radicals during ischaemia and reperfusion. *Clin Exp Pharmacol Physiol* 23: 700-708, 1996.
316. Schultz HD, Ustinova EE. Capsaicin receptors mediate free radical-induced activation of cardiac afferent endings. *Cardiovasc Res* 38: 348-355, 1998.
317. Schwartz PJ, Pagani M, Lombardi F, Malliani A, Brown AM. A cardiocardiac sympathovagal reflex in the cat. *Circ Res* 32: 215-220, 1973.
318. Schweinhardt P, Kalk N, Wartolowska K. Investigation into the neural correlates of emotional augmentation of clinical pain. *Neuroimage* 40: 759-766, 2008.
319. Sengupta JN. Esophageal sensory physiology. GI Motility online (2006). doi:10.1038/gimo16.
320. Serebro HA. The prognostic significance of the viscerocardiac reflex phenomenon. *S Afr Med J* 50: 769-772, 1976.
321. Sharkey KA, Sobrino JA, Cervero F. Evidence for a visceral afferent origin of substance P-like immunoreactivity in lamina V of the rat thoracic spinal cord. *Neuroscience* 22: 1077-1083, 1987.
322. Shepard JD, Barron KW, Myers DA. Corticosterone delivery to the amygdala increases corticotropin-releasing factor mRNA in the central amygdaloid nucleus and anxiety-like behavior. *Brain Res* 861: 288-295, 2000.
323. Sheps DS, Creed F, Clouse RE. Chest pain in patients with cardiac and noncardiac disease. *Psychosom Med* 66: 861-867, 2004.
324. Sherlock S. *Diseases of the Liver and Biliary System*. Oxford, UK: Blackwell, 1981.
325. Shin YK, Sohn UD, Choi MS, Kum C, Sim SS, Lee MY. Effects of rutin and harmaline on rat reflux oesophagitis. *Auton Autocoid Pharmacol* 22: 47-55, 2002.
326. Shriver JE, Stein BM, Carpenter MB. Central projections of spinal dorsal roots in the monkey: I. Cervical and upper thoracic dorsal roots. *Am. J. Anat* 123: 27-74, 1968.
327. Sleight P, Widdicombe JG. Action potentials in fibres from receptors in the epicardium and myocardium of the dog's left ventricle. *J Physiol (Lond)* 181: 235-258, 1965.
328. Steagall RJ, Sipe AL, Williams CA, Joyner WL, Singh K. Substance P release in response to cardiac ischemia from rat thoracic spinal dorsal horn is mediated by TRPV1. *Neuroscience* 214: 106-119, 2012.
329. Sugiura Y, Terul N, Hosoya Y. Difference in distribution of central terminals between visceral and somatic unmyelinated (C) primary afferent fibers. *J Neurophysiol* 62: 834-840, 1989.
330. Svensson O, Stenport G, Tibbling L, Wranne B. Oesophageal function and coronary angiogram in patients with disabling chest pain. *Acta Med Scand* 204: 173-178, 1978.
331. Sylvén C, Beermann B, Edlund A, Lewander R, Jonzon B, Mogensen L. Provocation of chest pain in patients with coronary insufficiency using the vasodilator adenosine. *Eur Heart J* 9(Suppl. N): 6-10, 1988.
332. Sylvén C, Beermann B, Jonzon B, Brandt R. Angina pectoris-like pain provoked by intravenous adenosine in healthy volunteers. *Br Med J* 293: 227-230, 1986.
333. Sylvén C, Borg G, Brandt R, Beermann B, Jonzon B. Dose-effect relationship of adenosine provoked angina pectoris like pain—a study of the psychophysical power function. *Eur Heart J* 9: 89-91, 1988.

334. Sylvén C. Angina pectoris. Clinical characteristics, neurophysiological and molecular mechanisms. *Pain* 36: 145-167, 1989.
335. Szallasi A. Autoradiographic visualization and pharmacological characterization of vanilloid (capsaicin) receptors in several species, including man. *Acta Physiol Scand* 629 (suppl.): 1-68, 1995.
336. Szallasi ABlumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol Rev* 51: 159-212, 1999.
337. Takeuchi Y, Uemura M, Matsuda K, Matsushima R, Mizuno N. Parabrachial nucleus neurons projecting to the lower brainstem and the spinal cord. A study in the cat by the Fink-Heimer and the horseradish peroxidase methods. *Exp Neural* 70: 403-413, 1980.
338. Tanimoto T, Takeda M, Matsumoto S. Suppressive effect of vagal afferents on cervical dorsal horn neurons responding to tooth pulp electrical stimulation in the rat. *Exp Brain Res* 145: 468-479, 2002.
339. Thames MD, Abboud FM. Reflex inhibition of renal sympathetic nerve activity during myocardial ischemia mediated by left ventricular receptors with vagal afferents in dogs. *J Clin Invest* 63: 395-402, 1979.
340. Thames MD, Klopfenstein HS, Abboud FM, Mark AL, Walker JL. Preferential distribution of inhibitory cardiac receptors with vagal afferents to the inferoposterior wall of the left ventricle activated during coronary occlusion in the dog. *Circ Res* 43: 512-519, 1978.
341. Thoren PN. Left ventricular receptors activated by severe asphyxia and by coronary artery occlusion. *Acta Physiol Scand* 85: 455-463, 1972.
342. Thoren PN. Activation of left ventricular receptors with non-medullated vagal afferent fibers during occlusion of a coronary artery in the cat. *Am J Cardiol* 37: 1046-1051, 1976.
343. Thoren PN. Characteristics of left ventricular receptors with non-medullated vagal afferents in cats. *Circ Res* 40: 415-421, 1977.
344. Thoren PN. Role of cardiac vagal C-fibers in cardiovascular control. *Rev Physiol Biochem Pharmacol* 86: 1-94, 1979.
345. Tjen-A-Looi S, Pan H-L, Longhurst JC. Endogenous bradykinin activates ischaemically sensitive cardiac visceral afferents through kinin B2 receptors in cats. *J Physiol (Lond)* 510: 633-641, 1998.
346. Tzukert A, Hasin Y, Sharav Y. Orofacial pain of cardiac origin. *Oral Surg Oral Med Oral Pathol* 51: 484-486, 1981.
347. Uchida Y, Murao S. Excitation of afferent cardiac sympathetic nerve fibers during coronary occlusion. *Am J Physiol* 226: 1094-1099, 1974a.
348. Uchida Y, Murao S. Potassium induced excitation of afferent cardiac sympathetic nerve fibers. *Am J Physiol* 226: 603-607, 1974b.
349. Uchida Y, Murao S. Afferent sympathetic nerve fibers originating in the left atrial wall. *Am J Physiol* 227: 753-758, 1974c.
350. Uchida Y, Murao S. Bradykinin induced excitation of afferent cardiac sympathetic nerve fibers. *Jpn Heart J* 15: 84-91, 1974d.
351. Uchida Y, Murao S. Acid-induced excitation of afferent cardiac sympathetic nerve fibers. *Am J Physiol* 228: 27-33, 1975.
352. Ustinova EE, Schultz HD. Activation of cardiac vagal afferents by oxygen-derived free radicals in rats. *Circ Res* 74: 895-903, 1994.
353. Vance WH, Bowker RC. Spinal origins of cardiac afferents from the region of the left anterior descending artery. *Brain Res* 258: 96-100, 1983.
354. Van Der Wall AC, Becker AE, Van Der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation* 89: 36-44, 1994.
355. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care* 26: 1553-1579, 2003.
356. Wagner R, Myers RR. Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. *NeuroReport* 7: 2897-2901, 1996.
357. Walker JL, Thames MD, Abboud FM, Mark AL, Klopfenstein HS. Preferential distribution of inhibitory cardiac receptors in left ventricle of the dog. *Am J Physiol* 235: H188-H192, 1978.
358. Wang CC, Westlund KN. Responses of rat dorsal column neurons to pancreatic nociceptive stimulation. *NeuroReport* 12, 2527-2530, 2001.
359. Wang J, Gu C, Al-Chaer ED. Sex hormones modulate the role of the postsynaptic dorsal column (PSDC) pathway in visceral pain. Program No. 171.14. *Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience.* Online, 2008.
360. Watkins LR, Goehler LE, Relton J, Brewer MT, Maier SF. Mechanisms of tumor necrosis factor-alpha (TNF-alpha) hyperalgesia. *Brain Res* 692: 244-250, 1995.
361. Watkins LR, Maier SF. Beyond neurons: Evidence that immune and glial cells contribute to pathological pain states. *Physiol Rev* 82: 981-1011, 2002.
362. Webb SW, Adgey AA, Pantridge JF. Autonomic disturbances at onset of acute myocardial infarction. *Br Med J Clin Res* 3: 89-92, 1972.
363. Webster KE, Kemplay SK. Distribution of primary afferent fibres from the forelimb of the rat to the upper cervical spinal cord in relation to the location of spinothalamic neuron populations. *Neurosci Lett* 76: 18-24, 1987.
364. Westlund KN, Bowker RM, Ziegler MG, Coulter JD. Origins and terminations of descending noradrenergic projections to the spinal cord of the monkey. *Brain Res* 292: 1-16, 1984.
365. Westlund KN, Coulter JD. Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in the monkey: Axonal transport studies and dopamine hydroxylase neurocytochemistry. *Brain Res Rev* 2: 235-264, 1980.
366. White FA, Bhangoo SK, Miller RJ. Chemokines: Integrators of pain and inflammation. *Nat Rev Drug Discov* 4: 834-844, 2005.
367. White JC, Bland EF. The surgical relief of severe angina pectoris. *Medicine (Baltimore* 27: 1-42, 1948.
368. White JC, Garrey WE, Atkins, JA. Cardiac innervation: Experimental and clinical studies. *Arch Surg* 26: 765-786, 1933.
369. Willis WD, Trevino DL, Coulter JD, Maunz RA. Responses of primate spinothalamic tract neurons to natural stimulation of hindlimb. *J Neurophysiol* 37: 358-372, 1974.
370. Woolf CJ, Salter MW. Neuronal plasticity: Increasing the gain in pain. *Science* 288: 1765-1769, 2000.
371. Woolf CJ, Wiesenfeld-Hallin Z. Substance P and calcitonin-gene related peptide synergistically modulate the gain of the nociceptive flexor withdrawal reflex in the rat. *Neurosci Lett* 66: 226-230, 1986.
372. Wright RA, McClave SA, Petruska J. Does physiologic gastroesophageal reflux affect heart rate or rhythm? *Scand J Gastroenterol* 28: 1021-1024, 1993.
373. Wu M, Komori N, Qin C, Farber JP, Linderoth B, and Foreman RD. Sensory fibers containing vanilloid receptor-1 (VR-1) mediate spinal cord stimulation-induced vasodilation. *Brain Res* 1107: 177-184, 2006.
374. Xu XJ, Dlasgaard CJ, Wiesenfeld-Hallin Z. Spinal substance P and N-methyl-D-aspartate receptors are co-activated in the induction of central sensitization of the nociceptive flexor reflex. *Neuroscience* 51: 641-648, 1992.
375. Yezierski RP, Broton JG. Functional properties of spinomesencephalic tract (SMT) cells in the upper cervical spinal cord of the cat. *Pain* 45: 187-196, 1991.
376. Yezierski, RP, Culberson, JL, Brown, PB. Cells of origin of propriospinal connections to cat lumbosacral gray as determined with horseradish peroxidase. *Exp Neurol* 69: 493-512, 1980.
377. Yezierski RP, Schwartz RH. Response and receptive-field properties of spinomesencephalic tract cells in the cat. *J Neurophysiol* 55: 76-96, 1986.
378. Zahner MR, Li D-P, Chen SR, Pan H-L. Cardiac vanilloid receptor 1-expressing afferent nerves and their role in the cardiogenic sympathetic reflex in rats. *J Physiol* 551: 515-523, 2003.
379. Zamir N, Segal M. Hypertension-induced analgesia: Changes in pain sensitivity in experimental hypertensive rats. *Brain Res* 160: 170-173, 1979.
380. Zamir N, Shuber E. Altered pain perception in hypertensive humans. *Brain Res* 201: 471-474, 1980.
381. Zhang J, Chandler MJ, Miller KE, Foreman RD. Cardiopulmonary spinal sympathetic afferent input does not require dorsal column pathways to excite C1-C3 spinal cells in rats. *Brain Res* 771: 25-30, 1997.
382. Zhang J, Chandler MJ, Foreman RD. Cardiopulmonary sympathetic and vagal afferents excite C1-C2 propriospinal cells in rats. *Brain Res* 969: 53-58, 2003.