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# Neuromodulation of cardiac pain and cerebral vasculature: Neural mechanisms

## ■ ABSTRACT

Research using animal models has helped elucidate the neural mechanisms of angina pectoris, sensitization of cardiac nociceptive stimuli, and neuromodulation of cardiac pain and cardiovascular function. Findings over the last 2 decades include evidence of convergence of visceral-somatic input to spinothalamic cells and a major role for the vagus nerve in spinal cord processing. Stress-related glucocorticoids may manipulate amygdala function, inducing hypersensitivity to nociceptive input from the heart via central sensitization of upper thoracic spinal neuronal activity. Spinal cord stimulation may have therapeutic effects, although the underlying mechanism is unclear.

**T**he cardinal symptoms of angina pectoris—chest pain and pain that may radiate to either arm or the neck and jaw—are well recognized. The visceral characteristics of anginal pain are also familiar; for example, referral to somatic structures, pain that is diffuse and poorly localized, skin and deep tissue tenderness, enhanced autonomic reflexes such as sweating and vasomotor symptoms, and muscular rigidity.

The neurologic mechanisms that explain the manifestations of angina pectoris are less well clarified, and are targets of active research. Our research into the neuromodulation of cardiovascular function over the last 2 decades has produced results that may have clinical implications and others that have raised new questions. This article summarizes some of our key

findings from studies of neural mechanisms of angina pectoris, central sensitization of cardiac nociceptive stimuli, and the neuromodulation of cardiac pain, with a focus on processing in the spinal cord.

## ■ NEURAL MECHANISMS OF ANGINA PECTORIS

Cells of the spinothalamic tract form a sensory pathway that transmits afferent information to the thalamus.<sup>1</sup> One of our research objectives was to examine how these cells process information when the heart is exposed to noxious stimuli.

### Thoracic spinal processing

The animal model for our early studies was an anesthetized primate. The afferent nerves were activated in one of two ways: either the coronary artery was occluded or bradykinin and algescic chemicals were injected into the pericardial sac or left atrial appendage. Recorded activity was then made from the spinothalamic tract cells in the T1-T5 and C5-C6 segments.<sup>1</sup> We found convergence of visceral and somatic input, generally to the chest and upper arm. The finding was consistent with the observation that pain from angina commonly occurs in proximal somatic fields. No visceral input was evident in cells in C7-C8, where the somatic effects are primarily distal—to the hand, for example.

### Upper cervical processing

It is known that some patients experience angina pectoris as neck and jaw pain. The dental literature has shown that what is initially considered to be a toothache occasionally turns out to be angina and coronary artery disease.<sup>2</sup> Clinical literature from the late 1940s observed that despite the use of sympathectomy to relieve angina pectoris, neck and jaw pain continued or developed.<sup>3,4</sup> This pain was attributed to transmission of nociceptive information in vagal afferent fibers, commonly thought to transmit innocuous cardiac sensory information.

When we recorded activity from spinothalamic tract cells in the C1-C2 region to observe the effect

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of cardiac nociceptive stimulation, we demonstrated a major role for the vagus nerve.<sup>1</sup> Injection of saline into the heart had no effect in the C1-C2 region, but injection of algescic chemicals into the pericardial sac caused significant activity that disappeared after transection of the vagus nerve. This finding suggested that vagal afferent fibers ascend into the nucleus tractus solitarius of the medulla and either directly or indirectly modulate the C1-C2 neurons, which also receive converging somatic information from the neck and jaw region.<sup>5</sup>

### ■ CENTRAL SENSITIZATION OF CARDIAC NOCICEPTIVE STIMULI

Clinical studies suggest that anxiety and depression are prevalent in patients suffering from chest pain with and without underlying cardiac disease.<sup>6</sup> Anxiety and/or stress increases circulating levels of corticosteroids, which can act on the glucocorticoid receptors in the amygdala, particularly in the central area.<sup>7</sup> The amygdala plays a pivotal role in transforming chronic stressful stimuli into behavioral, visceral, and autonomic responses.<sup>8</sup>

Previous studies have shown that corticosteroids upregulate expressions of corticotropin-releasing factor in the central nucleus of the amygdala and increase indices of anxiety.<sup>7,9</sup> They are also associated with hypersensitivity in visceromotor responses to colorectal distention<sup>10</sup> and sensitize lumbosacral spinal neurons to colorectal and urinary bladder distention.<sup>11,12</sup> We therefore hypothesized that glucocorticoids manipulate amygdala function, inducing hypersensitivity to nociceptive input from the heart through the modulation of upper thoracic spinal neuronal activity.

To examine the impact of stress on the nervous system when the heart is exposed to noxious stimuli, we assessed the effect of chronic activation of the amygdala on the T3-T4 spinal neurons and on C1-C2 propriospinal neurons. Fisher 344 rats were selected for this study because of their relatively low level of anxiety-related behavior.<sup>9</sup> Micropellets of crystalline corticosterone or cholesterol (30 µg, used as a control) were implanted in the central nucleus of the amygdala. After 7 days, the corticosterone-implanted, but not the cholesterol-implanted, animals displayed high-anxiety behavior, as determined with an elevated plus maze.<sup>7</sup>

The responses of T3-T4 spinal neurons to intrapericardial injections of the algescic chemical bradykinin were compared in the corticosterone- and cholesterol-implanted rats. Compared with cholesterol-implanted

animals, the duration of activity in response to the noxious cardiac stimulus was significantly longer in the corticosterone-implanted rats; in addition, activity 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. Long-lasting excitatory neuronal activity is associated with intense pain and hypersensitivity, while short-lasting neurons are associated with a more acute response. The number of neurons with large field sizes in the corticosterone-implanted animals also increased, which is another indication of sensitization.

To study the role of the propriospinal pathway from C1-C2 segments in transmitting information from the amygdala to the thoracic spinal cord, we stimulated the central nucleus of the amygdala, which created a burst activity in T2-T4 spinal neurons that ended when the stimulus was removed. We then exposed the C1-C2 and C5-C6 spinal cord segments to ibotenic acid, which disrupts cell function but does not affect axons, and repeated the amygdala stimulation. Overall, the responses of 65% of the T2-T4 cells tested by amygdala stimulation were eliminated after C1-C2 cell disruption, but none of the neuronal responses to amygdala stimulation were eliminated after ibotenic acid was applied to the C5-C6 segments. The results suggest that C1-C2 plays a role in transmitting information from the amygdala to the T3-T4 neurons, and that there is a small direct pathway between the two areas (Figure 1).

### ■ NEUROMODULATION OF CEREBROVASCULATURE AND CARDIAC PAIN

#### Neuromodulation of cerebral blood flow

Spinal cord stimulation is used to treat several cerebrovascular disorders, including cerebral ischemia, focal cerebral ischemia, stroke, postapoplectic spastic hemiplegia, and prolonged coma (see Yang et al<sup>13</sup> for citations that address these pathologies). There is no clear explanation for its therapeutic effect; mechanisms being investigated include changes in cerebral blood flow and processing of nociceptive information.

To assess the effect of spinal cord stimulation on cerebral blood flow, we exposed the C1-C2 area of an anesthetized rat, stimulated the area with a ball electrode, and used laser Doppler flow probes to measure the blood flow on the surface of the cortex bilaterally.<sup>13</sup> The stimulus parameters were 30%, 60%, and 90% of motor threshold; the threshold was determined by gradually increasing the intensity of spinal

cord stimulation until the neck muscles contracted. Blood flow increased on both sides with increasing stimulation intensities.<sup>13</sup>

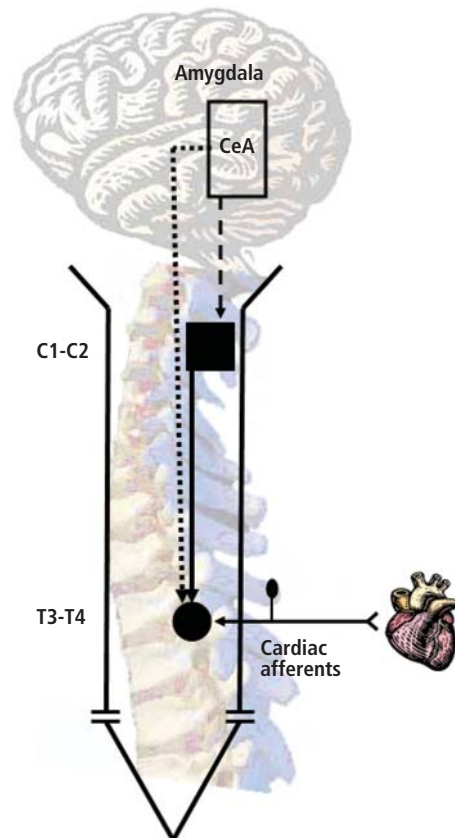
Other studies have evaluated cerebral blood flow but did not measure change in cerebrovascular resistance. We observed that spinal cord stimulation—particularly at 60% and 90% of motor threshold—increased blood flow and reduced resistance to spinal cord stimulation on the dorsal columns at C1, both ipsilaterally and contralaterally.

In other tests, cerebral blood flow and vascular resistance to spinal cord stimulation were not changed after transection of the spinal cord at the C6-C7 segments. These results suggested that information was not being transmitted to the sympathetic nervous system via the thoracic spinal cord. We applied ibotenic acid to C1-C2 to assess whether the underlying stimulated neurons affected cerebral blood flow; there was no significant change. On the other hand, a small cut in the dorsal column rostral to the stimulation site caused significantly reduced cerebral blood flow and vascular resistance, indicating that the dorsal columns function in an ascending manner to produce the vasodilation in the cerebral cortex.<sup>13</sup>

Capsaicin-sensitive sensory nerves, which contain transient receptor potential vanilloid-1 (TRPV1) receptors, may have a role in spinal cord stimulation-induced vasodilation. TRPV1 receptors are nonselective cation channels activated by capsaicin, heat, and hydrogen ions.<sup>14</sup> Activation, which causes an influx of cations and release of calcitonin gene-related peptide (CGRP) and substance P, is related to the pathogenesis of inflammation and hypertension. To examine the potential role played by capsaicin-sensitive sensory nerves, we administered resiniferatoxin (RTX), an ultrapotent capsaicin agonist; RTX specifically targets and desensitizes TRPV1-containing sensory fibers.<sup>13,15</sup> Administration either intravenously or by direct application to the spinal cord results in a 15- to 20-minute period of sensitization followed by several hours of desensitization; if exposure lasts for several days, the nerves are destroyed.

Intrathecal administration of RTX to the spinal cord resulted in no significant change in cerebral blood flow. However, intravenous administration resulted in significantly decreased cerebral blood flow and decreased resistance, suggesting a role for TRPV1 receptors in cerebral blood flow.<sup>13</sup>

There may be a connection between spinal cord stimulation at C1 and vasodilation of the cortex. The literature suggests that spinal cord stimulation activates the dorsal column nuclei<sup>16</sup>; we found evidence



**FIGURE 1.** Proposed glucocorticoid-activated descending pathways from the central nucleus of the amygdala (CeA) that may produce central sensitization of the upper thoracic spinal neurons receiving cardiac nociceptive information. The descending information may be transmitted directly (dotted line) to the upper thoracic neurons or in part through activation (dashed line) of propriospinal neurons in the C1-C2 segments (solid line). It should be pointed out that the dotted line also represents neurons from the CeA that may send projections to several brainstem nuclei, which then send axons to the spinal cord.

of this in our laboratory when we recorded activity from cells in the cuneate and gracilis nuclei after spinal cord stimulation. There is also a possible pathway between the dorsal column, the rostral ventrolateral medulla, and the sphenopalatine ganglion that influences vasodilation.<sup>17-20</sup> Although not yet clearly defined, evidence suggests a connection between spinal cord stimulation and transmission of this information through the dorsal columns to influence vasodilation.<sup>17-20</sup>

### Neuromodulation of thoracic spinal processing of cardiac nociceptive information

Stimulating the dorsal columns activates the large afferent fibers, which in turn activate neuronal mechanisms in the spinal cord gray matter. These mecha-

**TABLE 1**  
Clinical results of spinal cord stimulation (SCS)<sup>23</sup>

	Angina attacks/wk	Heart rate–systolic blood pressure product (beats/min × mm Hg)/1,000
Pre-SCS	30.9 ± 14.5	9.6 ± 1.9
Post-SCS	9.6 ± 8.2	14.1 ± 3.4
P value	< .01	< .01

nisms may be partly attributed to “gate control,” in which large afferent fibers can decrease the amount of information coming from the nociceptive afferent nerves to reduce the nociceptive sensation.<sup>15,21,22</sup> González-Darder et al<sup>23</sup> considered this mechanism in a study of 12 patients with unstable angina (Table 1). Upper cervical spinal cord stimulation resulted in a decreased number of anginal episodes per week and an improved rate-pressure product (heart rate × systolic blood pressure). Their findings suggest that stimulating the upper cervical region could achieve effects similar to those seen after stimulating the spinal cord at T2.

Using a rat model to assess the effects of spinal stimulation, we recorded T3 activity during dorsal column stimulation of either C8-T1 or C1-C2 segments. Activity was almost completely suppressed with C1-C2 stimulation during bradykinin injection into the pericardial sac. The results suggest that spinal cord stimulation suppresses the processing of nociceptive information.<sup>24</sup>

Stimulating the spinal cord at C8-T1 also suppresses the effect of bradykinin. One possible mechanism for this effect is that spinal cord stimulation activates large afferent fibers; GABAergic connections in the superficial dorsal horn may suppress the processing of information in the spinothalamic tract neurons.<sup>22,25</sup>

## SUMMARY

Our investigations have generated information about afferent input to the spinothalamic tract cells, the effects of glucocorticoids on amygdala function, and possible therapeutic mechanisms of spinal cord stimulation.

We have demonstrated convergence of viscerosomatic input in spinothalamic cells. There is virtually no viscerocardiac input at the C7-C8 region, but there is input at C5-C6. Vagal afferent activity is the major source of input at the C1-C2 region;

vagal stimulation also affects propriospinal neurons in this region. Vagal nerve stimulation may have a major role in processing in the upper cervical spinal cord and may change the balance of processing in the supraspinal nuclei.

Glucocorticoids manipulate amygdala function by inducing hypersensitivity to nociceptive input from the heart through central sensitization of upper thoracic spinal neuronal activity. Descending information from the amygdala depends, in part, on the C1-C2 propriospinal pathway.

Spinal cord stimulation at C1-C2 or C8-T1 can activate inner neuronal mechanisms that may involve GABA, modulating the wide dynamic range of neurons that are part of the spinothalamic tract.

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