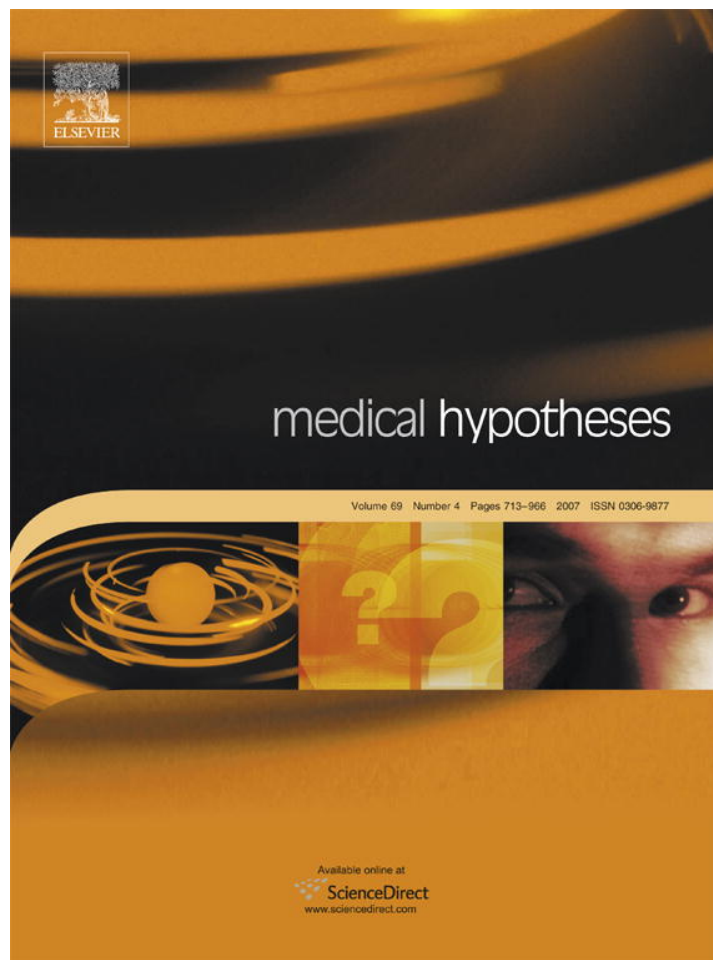


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# Stellate ganglion block may relieve hot flashes by interrupting the sympathetic nervous system

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**Summary** Stellate ganglion block is routinely used in pain clinics. The mechanism of action of the stellate ganglion block is uncertain; the most common explanation is that it produces peripheral vasodilation, resulting in neural inhibition in the ganglion's sphere of innervation. However, the wide range of conditions that have been reported to respond favorably to stellate ganglion block suggest that its effectiveness may not be solely the result of increased blood flow nor restricted just to its sphere of innervation. We have found that stellate ganglion block is effective in the treatment of hot flashes in postmenopausal women, as well as those with estrogen depletion resulting from breast cancer treatment. Based on evidence that hot flashes may be centrally mediated and that the stellate ganglion has links with the central nervous system nuclei that modulate body temperature, we hypothesize that the stellate ganglion block provides relief of hot flashes by interrupting the central nervous system connections with the sympathetic nervous system, allowing the body's temperature-regulating mechanisms to reset. If this mechanism can be confirmed, this would provide women with intractable hot flashes with an effective, potentially long-lasting means of relieving their symptoms, and potentially widen the range of indications for stellate ganglion block to include other centrally mediated syndromes.

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## Hypothesis

The stellate ganglion is sympathetic ganglion located anterior to and below the transverse process of C6 and C7 and ventral or ventromedial to the vertebral artery. Through direct innervation it has

effects on the head, neck, heart, and upper extremities. Stellate ganglion block is a selective sympathetic block that influences ipsilateral head, neck, upper extremity, and the upper part of the thorax. The stellate ganglion block is frequently used in pain clinics for the treatment of migraines, atypical facial pain, upper extremity pain, and complex regional pain syndrome of the chest. Efficacy of the stellate ganglion block is usually assessed by the presence of Horner's syndrome and

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anhidrosis. In Japan stellate ganglion block has a much wider range of indications and is used for many systemic diseases including diseases of the immune and endocrine systems [1].

The mechanism of action of the stellate ganglion block is not totally understood, but may involve peripheral vasodilation, resulting in neural inhibition in the ganglion's sphere of innervation [1]. However, the wide ranges of conditions that respond favorably to stellate ganglion block suggest that its effectiveness may not be solely the result of increased blood flow, and also may be effective in conditions beyond its immediate sphere of innervation.

We have found that stellate ganglion block is effective in the treatment of hot flashes in postmenopausal women [2], as well as those with estrogen depletion resulting from breast cancer treatment. To date 15 women have been injected from the right side at the C6 ganglion. All had at least an 80% decrease in hot flashes for two weeks following the stellate ganglion blockade. One woman was injected on the left side at C6 without effect. Five of the women had a history of breast cancer, with four of them receiving hormone treatment, i.e., the estrogen blocking drug tomaxifen (2 patients) or adraril (2 patients). One refused estrogen blocking treatment due to severe hot flashes prior to the initiation of the therapy and elected to have chemotherapy instead. All 5 had at least 80% diminution of hot flashes from the blockade except for the left sided injection. The response of the women who had estrogen blocking treatment to stellate ganglion blockade was not different from those patients who were treated for menopause induced hot flashes [2].

There is evidence to suggest that the sympathetic nervous system is involved in the production of hot flashes [3,4]. Based on these observations and on recent descriptions of the stellate ganglion's neural connections we hypothesize that the stellate ganglion block provides relief of hot flashes by interrupting the sympathetic nervous system, perhaps by allowing the body's temperature-regulating mechanisms to reset.

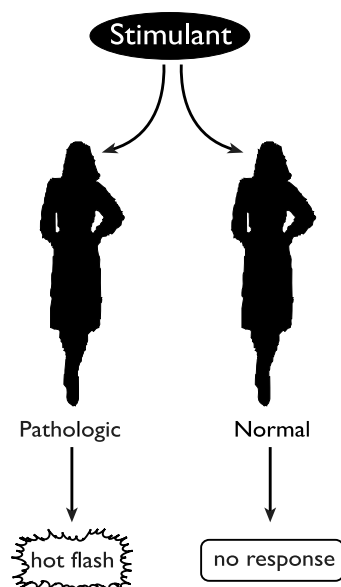
### Evidence of central sympathetic involvement in hot flashes

The symptoms of hot flashes that occur in menopausal women are characteristic of a heat-dissipation response and consist of sudden sensations of intense heat with sweating, flushing, and peripheral vasodilation. The exact pathogenesis of hot flashes has not been entirely

elucidated, but there appears to be an alteration in the homeostatic thermoregulatory system. The underlying physiological systems implicated in the etiology of hot flashes include the sympathetic nervous system and the hypothalamus, estrogen therapy, and norepinephrine neurotransmitter system.

According to Freedman [3,4], hot flashes result from the narrowing of the thermoneutral zone where thermoregulatory adjustments do not usually occur. Core temperature is regulated between upper thresholds for sweating and vasodilation, and lower thresholds for shivering and vasoconstriction. Between these thresholds is the thermoneutral zone where thermoregulatory adjustments do not occur. In the past, hot flashes were attributed to a downward resetting of the upper threshold for sweating; however, recent evidence points to an alteration in the thermoneutral zone such that it basically is nonexistent in women who are symptomatic for hot flashes. Therefore, small temperature elevations preceding hot flashes act within the now nonexistent thermoneutral zone, leading to the triggering of a hot flash. This hypothesis is supported by data presented in a series of papers conducted and reviewed by Freedman [3–5]. In these experiments, women who were symptomatic or asymptomatic for hot flashes were used. Ingested telemetry devices were used to measure core body temperature. He found that the core body temperature is elevated in symptomatic patients just prior to the onset of hot flashes when the patient is awake, walking, or asleep. In addition, he found that both the sweating threshold is reduced and the shivering threshold elevated in symptomatic women, but not asymptomatic women. These data support the hypothesis that the thermoneutral zone is narrowed or nonexistent in symptomatic women (see Fig. 1).

Women suffering from hot flashes show elevations in central sympathetic activation. In concert with the increases in core body temperature that precede hot flashes there is a significant increase in the plasma levels of a metabolite of brain norepinephrine, but not of a peripheral metabolite [6,7]. No peripheral vasoconstriction is noted, and metabolic rate is increased only after the rise in core temperature. Freedman [6] concluded that the core body temperature increases are probably driven by a central noradrenergic mechanism, not by peripheral vasoconstriction or increased metabolic rate [6]. In support of this increase in central sympathetic tone during hot flashes, several studies have shown that clonidine, an  $\alpha_2$ -adrenergic agonist that reduces brain norepinephrine, is an



**Figure 1** Differential effect of thermal stimulants on patients symptomatic or asymptomatic for hot flashes. The thermoneutral zone is narrowed or nonexistent in symptomatic women.

effective treatment for postmenopausal or breast cancer-therapy-related hot flashes [8–12]. Injection of the  $\alpha_2$ -adrenergic antagonist yohimbine leads to an increase in norepinephrine brain levels and provokes hot flashes in symptomatic women, an effect that is reduced by clonidine [12]. The authors concluded that the core body temperature increases are probably driven by a central noradrenergic mechanism, not by peripheral vasoconstriction or increased metabolic rate. Taken together these data implicate an increase in central sympathetic activation and brain norepinephrine levels in the initiation of hot flashes in symptomatic women that occurs concordant with the increase in core body temperature.

Evidence for a central mechanism for hot flashes may also be provided by some treatments that are known to be effective in treating hot flashes. Estrogen, for example, has long been known to suppress or eliminate hot flashes in postmenopausal women. A recent study by Freedman and Blacker [13] showed significant increases in core body temperature sweating threshold in postmenopausal women with hot flashes taking oral 17 $\beta$ -estradiol. The mechanism by which estrogen exerts its effects is still uncertain; however, Vongpatanasin et al. [14], in a randomized placebo-controlled crossover study evaluating the protective effect of transdermal estrogen on blood pressure, found that transdermal estrogen therapy lowered the basal rate of sympathetic nerve discharge by 30% after 8

weeks. The authors concluded that their results supported a hypothesis of a sympathetic inhibitory effect of estrogen.

The hypothalamus is the brain area that is primarily in control of thermoregulatory mechanisms, as indicated from results from both animals and humans (reviewed [15,16]). The control of temperature however is complex and involves the integration of information from the periphery that is conveyed to the brain. Many studies indicate that human brain regions that respond to change in skin temperature to regulate homeostatic responses to changes in environmental temperature include such areas as the somatosensory cortex, insula cortex, anterior cingulate, thalamus, and hypothalamus [17–19].

Freedman et al. [20], in a controlled study of postmenopausal women with hot flashes, used functional magnetic resonance imaging to identify regions of brain activation associated with hot flashes and with sweating in women without hot flashes. Surprisingly, the hypothalamus did not emerge as central region of activation associated with hot flash. They found that the insula and anterior cingulate cortex showed significant activation during hot flashes. Asymptomatic women also showed activation of the anterior cingulate and the superior frontal gyrus during sweating, but not the insula cortex. Perhaps the insular cortex can be viewed as the gateway of the sympathetic system to the brain. The authors concluded that the insular cortex is associated with the “rush of heat” described by women with hot flashes and therefore plays a role in thermosensory integration. Activation of the cingulated cortex, since it occurs in both symptomatic and asymptomatic women may be related to an affective component of thermosensation. Interestingly, estrogen treatment has also been indicated to increase neural activity in the insular cortex [21,22].

### Evidence that part of the effect of stellate ganglion block is centrally mediated

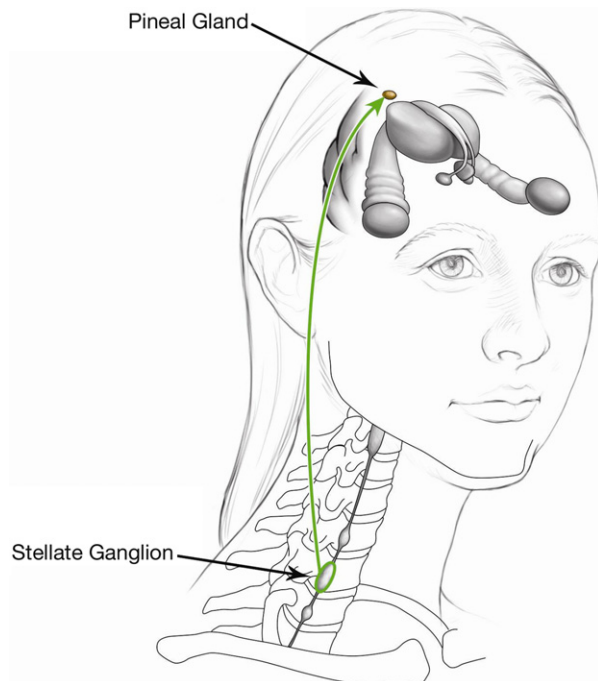
Other than hot flashes, there are other conditions known to respond favorably to stellate ganglion block that are thought to be centrally mediated. One such condition is complex regional pain syndrome (CRPS; also called reflex sympathetic dystrophy) [23]. In a review of CRPS, Bogduk reports that although some view the condition as psychoneurogenic, “most recent work favors a central mechanism” for both the sensory and autonomic features of the syndrome [24]. Shiraishi et al.

conducted a study of abnormalities of the central nervous system in patients with CRPS, comparing them with normal age-matched controls. Using positron emission tomography, they found that subjects with CRPS had increased glucose metabolism in the secondary somatosensory cortex, the mid-anterior and/or posterior cingulate cortex, the parietal and posterior parietal cortex, and the cerebellum, right posterior insular cortex, and right thalamus, while noting decreased metabolism in the prefrontal and primary motor cortex [25].

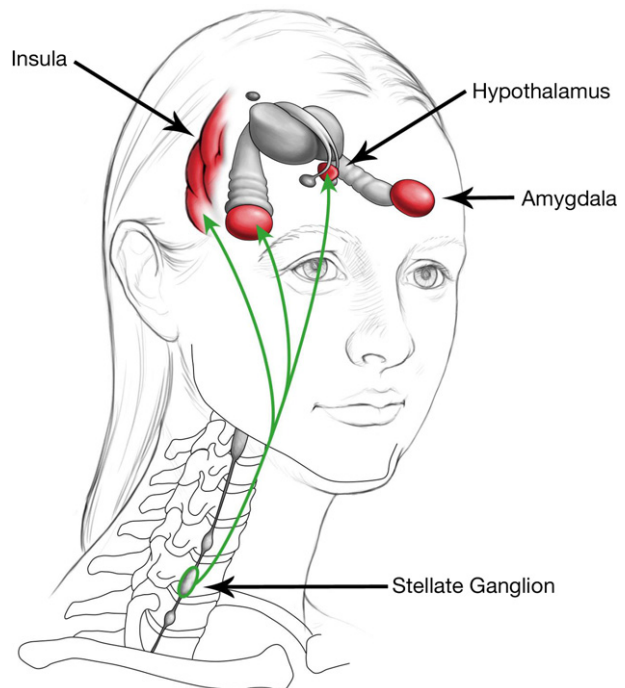
Uchida et al. recently [1] presented a hypothesis suggesting that stellate ganglion block may help to relieve melatonin-related dysrhythmias such as sleep disorders [1]. They theorize that such dysrhythmias are the result of chronically increased sympathetic nerve tone, which eventually causes decreased functioning of pinealocytes and leads to reduction of plasma melatonin levels. The stellate ganglion block, they suggest, may function by interrupting the sympathetic cycle, allowing the normal melatonin rhythm to be re-established (Fig. 2).

One of the most direct means for providing evidence of connections between two brain nuclei is the use of anatomical labeling techniques. Westerhaus and Loewy [26], in the course of mapping the

sympathetic nervous system related regions of the cerebral cortex used pseudorabies virus injections to identify connections of the stellate ganglion. Pseudorabies virus allows identification of neural pathway connections that are 2–3 synapses from the point of injection of the virus. In this manner, the use of pseudorabies virus injection is used to identify cortical areas connected to the stellate ganglion. In the early stage of infection (5 days), labeling is found in the hypothalamus and central nucleus of the amygdala. With slightly longer time labeling is found in lateral, basolateral, and medial amygdala. After 6–8 days, injections of the stellate ganglion produced extensive transneuronal labeling in the infralimbic, insular, and ventromedial temporal cortical regions. These data provide support for the potential of the stellate ganglion to interact with several key structures known to modulate core body temperature, i.e., the hypothalamus, amygdala, and regions of the prefrontal cortex, in particular the insular cortex (Fig. 3). These data then also correspond directly with the functional magnetic resonance imaging results



**Figure 2** Therapeutic effect of stellate ganglion block on sleep improvement. The neural connections between the stellate ganglion and the pineal gland may function to normalize melatonin rhythm.



**Figure 3** Therapeutic effect of the stellate ganglion block on generation of hot flashes. Neural connections between the stellate ganglion and the hypothalamus, amygdala and regions of the prefrontal cortex, in particular the insular cortex may be involved in the interruption the of the sympathetic nervous system allowing the body's temperature-regulating mechanisms to reset.

provided by Freedman et al. [20], showing that the insular cortex is activated during hot flashes and that the stellate ganglion provides neural input into this area.

Experiments that could be conducted to test this hypothesis would include MRI imaging prior to, during and following stellate ganglion block. These experiments should demonstrate stellate ganglion block leads to an activation of the insular cortex and perhaps hypothalamus. Additional experiments could include the measurement of the central and peripheral noradrenergic metabolites during stellate ganglion block. It would be expected that the norepinephrine levels normally increased during hot flashes would be decreased by the stellate ganglion block treatment and therefore there would be a selective decrease in the brain norepinephrine metabolite. In addition the use of ingested telemetry devices could be used to measure changes in core body temperature and the thermoneutral zone prior to and following the stellate block treatment. It would be expected that the thermoneutral zone would be increased by the treatment and that this increase would last as long as the effectiveness as the stellate block treatment does in the treatment of hot flashes.

## Conclusion

Based on the evidence summarized above, that hot flashes may be centrally mediated and due to an increased activity of central nervous system nuclei linked to the sympathetic nervous system and norepinephrine release, the hypothesis that the stellate ganglion block works to relieve hot flashes by interrupting the sympathetic nervous system seems to be a likely possibility. Further support is derived from other reports that stellate ganglion block is effective for other conditions known to be centrally mediated, such as CRPS. If this mechanism can be confirmed, this would provide women with intractable hot flashes with an effective, potentially long-lasting means of relieving their symptoms, and potentially widen the range of indications for stellate ganglion block to include other centrally mediated syndromes.

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