Chinese Journal of Physiology 52(5 Supplement): 345-357, 2009
DOI: 10.4077/CJP.2009.AMK043

Review

Somatosympathetic Reflex and Acupuncture-Related Analgesia

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Abstract

Both acute and chronic pains correspond to nociceptive substances (NSs), which are naturally produced and metabolized by the organism experiencing the pains. The accumulation of NSs in regional tissues triggers a series of pathophysiological reactions and initiates certain threats to the health and the quality of human life. Pharmacological intervention is the most popular treatment for pain relief, which is achieved by either reducing the production of NSs or blocking the transmission of nociceptive signals through the nervous system, but no drug has been developed for the elimination of NSs. Therefore, improving blood circulation to eliminate NSs in painful tissues is an alternative strategy for pain relief. Acupuncture has been proved to be effective for the treatment of certain kinds of pain, but the mechanisms therein remain unclear. The effectiveness of acupuncture analgesia is also variable owing to the uncertainty surrounding the mechanism and the poor standardization of the technique. There is some evidence that acupuncture may induce pain relief by changing the regional blood flow through somatosympathetic reflex (SSR). Therefore, when exploring the mechanisms of SSR in detail, it is helpful to clarify the mechanisms of acupuncture analgesia and to develop a more standardized and effective protocol for acupuncture analgesia. Increasing evidence has suggested that both sympathetic activity and stimulation-induced SSR are differentially controlled in an organ-specific and activity-dependent manner. Vasomotor outflow, which involves the regulation of impaired regional blood circulation, is also differentially controlled in response to specific somatic stimulation. Therefore, we vigorously review the relations between SSR and acupuncture-related analgesia so that we can develop a targeted pain therapy where in certain areas of the body undergo site-specific somatic stimulation, which in turn, can adjust the impaired regional blood circulation.

Key Words: somatosympathetic reflex, pain, analgesia, acupuncture, nociceptive substance, sympathetic nervous system, blood circulation

Introduction

Pain, a sensation of discomfort, is a basically protective mechanism for the survival of the organism. However, chronic pain has becomes a major threat to the health and the quality of human life worldwide. According to data from the WHO and the International Association for the Study of Pain, 1 in 5 adults suffers from chronic pain nowadays (62).

During recent years, our knowledge of pain mediators, of pain processing, and of nociceptive stimulation's effects on the function and structure of the nervous system has been growing enormously (103). Despite such achievements, pain treatment in patient care has not significantly improved. In addition, the approach to pain treatment has focused on pharmacological intervention, inducing a plethora of unexpected side effects. The development of cyclooxygenases-2 (COX-2) inhibitors exemplifies this recent trend in novel pharmacological pain killers (88).

All non-steroid anti-inflammatory drugs (NSAIDs) cause not only irritation, ulceration, bleeding, and perforation of the mucosal lining of the stomach (32),

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Received: June 19, 2009; Accepted: August 17, 2009.
 ISSN : 0304-4920. http://www.cps.org.tw

but also water retention owing to the deterioration of renal function (112). Vioxx and Bextra, the newly developed COX-2 NSAIDs, were hurriedly withdrawn from the world market after reports declared that these drugs significantly increased cardiovascular morbidity and mortality in comparison with conventional NSAIDs (67).

Injured tissues synthesize and release nociceptive substances (NSs) to trigger a series of tissue reactions including humoral and neural reactions, which are considered a tissue-repairing process and a signal of danger (44). The accumulation of NSs triggers a series of pathophysiological effects and may have certain harmful effects on the body. Generally, pharmacological intervention functions to reduce the production of NSs or to inhibit NS-induced nociceptive transmission through each level of the nervous system (15). But several adverse effects have been found in clinical usage of these medications (32, 67, 88, 112), and sometimes, impaired regional blood circulation may decrease the medications' effectiveness owing to reduced pharmacokinetic action. Thus, some physical therapies with fewer side effects have surfaced as alternatives for pain relief (1). Because physical therapy is considered less effective than pharmacological therapy, a question arises as to whether it is possible to develop a more effective method of pain-management physical therapy that has fewer and less serious side effects than the corresponding pharmacological therapy.

Acupuncture and moxibustion have been used in China and other Asian regions for nearly 3000 years (106). Increasing evidence supports the assertions that acupuncture and newly developed "transcutaneous neuromodulation"-related therapies are effective in treating certain kinds of pain (105). Even though acupuncture and related therapies have been proved to trigger a series of effects including the release of neurotransmitters, changes in neural plasticity, and the activation of c-fos in the neurons of related central neural circuits (61, 93, 113), the mechanism underlying acupuncture-induced analgesia remains unclear. Several hypotheses such as gate theory, endorphin theory, neural plasticity theory, and descending inhibitory theory have been proposed to explain the mechanisms of acupuncture analgesia (61, 96, 113). Most of these mechanisms concern pain inhibition, but the research tends to ignore noteworthy accompanying phenomena such as the improvement of blood circulation (in either ischemic or congestive conditions) after acupuncture treatment. Although somatosympathetic reflex (SSR) is thought to be relevant to the regulation of blood circulation in acupuncture, little is mentioned about the somatosympathetic hypothesis, except in segmental acupuncture.

Since NSs are naturally produced and metabolized by organisms, improving regional blood circulation to flush out the NSs seems to be an effective strategy for pain relief. Researchers would be much closer to developing a more effective method for enhancing the elimination of NSs as soon as the research field clarifies the mechanisms controlling regional blood flow in both physiological and pathological conditions. The sympathetic activity relative to each organ is not homogenous; therefore, it's difficult to adjust the sympathetic activity through pharmacological approaches, which are considered to be nonspecific and not targeted. A growing body of evidence points to the differential control of sympathetic outflow and SSR (49, 75), suggesting that stimulation of one body region may excite the sympathetic nerves innervating certain organs but may inhibit the sympathetic nerves innervating the other organs (13); therefore, one possible targeted therapy would rest on the selection of specific somatic stimulation sites. In the present work, we will focus on sympathetic reactions induced by somatic stimulation, especially the vasomotor control. The mechanisms of acupuncture analgesia concerning SSR are also discussed.

Pain and Blood Circulation

Impairment of blood circulation can take place in either acute injuries, manifested as tissue edema and extravasation of tissue fluid, or in chronic-ischemic situations, manifested as poor blood perfusion (34, 43). The impaired blood circulation in turn reduces the removal of NSs by the systemic route and then increases the accumulation of NSs in local tissues; therefore, nociceptive signaling, which produces pain sensation, is enhanced by the action of increasing level of NSs in local tissues. Improving the regional blood circulation can reduce the amount of NSs in local tissue, thereby diminishing not only the action of NSs but the intensity of pain, as well.

Nociceptive Substances (NSs)

NSs are produced by injured tissues and act on the nociceptive receptors on primary sensory afferents to initiate a series of events including local neurogenic inflammation, muscle contracture and ischemia, SSR, and pain perception in the brain (44).

NSs are initiators relative to pain and become the primary target in the development of pain-relief methods. Since the action of NSs on the sensory nervous system is the primary cause of pain and because the accumulation of NSs in local tissues can trigger sensations of pain in either acute or chronic pain, the development of alternative pain-relief strategies

should focus on the elimination of NSs.

All NSs are produced by organisms, whose enzyme systems can degrade and metabolize the NSs. The concentration of NSs in regional tissue depends on three factors: [1] the degree of inflammation or ischemia that relates to the amount of production; [2] the activity of enzyme that degrades NSs; and [3] the condition of blood circulation that relates to the elimination of NSs from local tissue. The removal of NSs includes both local degradation by enzymes and systemic degradation by washing into systemic blood.

Neurogenic Inflammation and Pain

Besides the innervation of sympathetic vasomotor efferents, nearly all segments of the vasculature are innervated by the peripheral terminals of sensory afferent neurons (34). Consequently, activation of nociceptive receptors can trigger both the modulation of sympathetic vasomotor activity and antidromic reflexes of sensory terminals in the vascular wall (30, 48). Activation of peripheral terminals of primary sensory afferent neurons releases bioactive substances that, in turn, act on several target cells in the periphery such as endothelial cells, mast cells, and immune cells to trigger regional inflammation, called neurogenic inflammation (43). Neurogenic inflammation is presented as redness and warmth (secondary to vasodilatation), swelling and edema (secondary to plasma extravasation), and local hypersensitivity (secondary to enhancement in the excitability of sensory neurons) (43).

Some mediators induce neurogenic inflammation by directly activating sensory nerve endings and by triggering neurotransmitter release, but other substances involve in the inflammatory process by sensitizing the receptors. Substance P (SP) and calcitonin gene-related peptide (CGRP) are regarded as the two major mediators of neurogenic inflammation. These neurotransmitters are produced and released by a subset of small dorsal root ganglion cells, which give rise to the thin myelinated Aδ and unmyelinated C fibers (33). Activation of primary afferent C fibers releases SP and CGRP in terminals peripherally and in the dorsal horn of the spinal cord centrally (48, 90).

Sensory neurons of a small diameter also contain cyclooxygenases (COX) and are capable of synthesizing and releasing prostaglandins (20, 97, 104). Two major prostaglandins, prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2), are released into both peripheral tissues and the spinal cord during tissue injury or inflammation (19) and contribute to the development of neurogenic inflammation and hypersensitivity. In addition, bradykinin and ATP also have been reported to sensitize small-diameter sensory neurons (4, 101, 107). The production and release of prostaglandins and bradykinin in the injured tissues cause subsequent chemotaxis of inflammatory cells and cytokine production, which in turn enhance the expression of COX-2 to make more prostaglandins.

Since the release and accumulation of NSs trigger neurogenic inflammation, clarifying what conditions and events regulate the release and metabolism of NSs is critically important to intervention in both acute and chronic inflammation. Tissue injury is the primary cause of neurogenic inflammation in which blood congestion, tissue edema, and tissue swelling are the major manifestations. Impairment of blood circulation stems from the compartment effect of tissue edema and swelling; therefore, both increased production and decreased elimination of NSs increase the concentration of NSs. The accumulation of NSs exacerbates pain, and NS-induced sensitization of sensory neurons triggers hyperalgia. It is concluded that both inhibiting the production and enhancing the elimination of NSs are effective in pain relief. Improving the impaired regional blood flow is an effective strategy for the elimination of NSs; therefore, the strategy is beneficial in pain treatment.

Ischemia and Pain

Regulatory events acting on distinct levels of vasculatures can affect the microcirculation not only in the delivery of oxygen and nutrients but also in the removal of metabolic waste. During muscle contraction, mechanical compression impedes arterial inflow and promotes venous return simultaneously, while passive stretch of resting muscle can restrict tissue perfusion and inhibit ascending vasodilation (60).

Myofascial pain is associated with poor blood perfusion and ischemia in affected muscle (59). The contracture and energy crisis mechanism has been proposed as a hypothesis for the pathogenesis of trigger points and myofascial pain (95, 102). Minor injury of muscle tissue induces the release of calcium ions from the endoplasmic reticulum of the muscle cell, and these ions trigger the contraction of muscle. The muscle contracture reduces the blood flow and suppresses the oxygen supply to the muscle, and the ischemia leads to release of various substances, mostly NSs, that sensitize the nociceptors and induce pain sensation.

Ischemia exaggerates the accumulation of NSs and induces the maintenance of pain; therefore, a vicious cycle develops. Since increasing regional blood flow is the only way to correct the ischemia of tissue, improving blood circulation is the most effective treatment in ischemia pain.

Differential Control of Sympathetic Outflow

Because sympathetic nervous system (SNS) controls blood vessels, a more rigorous exploration of the SNS-related differential-control mechanism could greatly strengthen the targeted improvement of impaired regional blood circulation. In this effort, Canon was the first to propose the "fight or flight" response to describe the functions of SNS; hence, SNS has been generally regarded as involving a global reaction in organisms' survival mechanisms. SNS was thought to antagonize the actions of the parasympathetic nervous system (PSNS) so that the organisms maintain their physiological functions in a homeostatic state (11). However, a growing body of knowledge supports that SNS acts differentially in an activity-dependent manner (75).

Pathophysiology of SNS and SSR

Animals must respond quickly to the changing environment. The quicker response is mediated by neural reactions, and the slower one is mediated by the hormonal system; therefore, organisms can maintain their physiological functions in a homeostatic status. Sympathetic nervous function (SNF) is involved in the regulation of almost all physiopathological functions of vital organs (37). Jänig and his coworkers have provided an overarching view on the organization and function of a variety of peripheral sympathetic efferents in the cat and rat (36, 38-41). They have characterized sympathetic efferent outflows such as [1] vasoconstrictors to muscle and viscera, [2] cutaneous vasoconstrictor, [3] muscular vasodilator, [4] cutaneous vasodilator, [5] sudomotor, [6] pilomotor, and [7] pupillo-motor (35).

In line with the somatomotor system, Jänig has proposed the hypothesis of the "spinal autonomic motor programs", which describes the integrative mechanism of spinal autonomic circuits for the control of autonomic target organs (35). The spinal autonomic circuits receive signals from supraspinal centers and infraspinal pathways consecutively, and a preprogrammed mechanism integrates these signals to create an autonomic response. The regulation of SNS is closely integrated with the regulation of the somatomotor system, and the coupling of somatomotor and sympathetic outflows from the spinal cord has been proved (14).

Normally, animals restore their physiological functions homeostatically by negative feedback mechanisms while being perturbed by external and internal stimuli (37). Certain situations can give rise to the development of inappropriate SNS reactions; therefore, the abnormal SNF may put the organism into a pathological condition restraining the organism from recovery. Many pathological conditions are associated with either overtly elevated SNF or abnormally suppressed SNF due to the development of a positive feedback loop that preserves a vicious cycle. Correction of such an abnormally high or low SNF can modify the pathological conditions in some circumstances. This biological phenomenon may open an opportunity to improve pathophysiological conditions through modulating the SNF.

Researchers could develop an effective strategy that rests on the mechanisms of SSR and that promotes recovery from pathological situations by means of sympathetic modulation. Some physical therapy such as acupuncture and moxibustion, transcutaneous electrical nerve stimulation (TENS), infrared treatment, low-energy lasers, massage, and hot packs have long been widely used in disease treatment and health maintenance. But only a vague correlation between these treatments and SSR is identifiable because these therapies usually cause a global effect that resists definition and measurement.

Differential Control of Sympathetic Outflow

Understanding the action model of the SNS is crucial for the study of SSR. According to the earliest pertinent concept, the SNS is a monolithic effector responding globally to life-threatening challenges and protecting cerebral perfusion in a significant injury. In contrast, the PSNS is involved in the recovery from such challenges and is manifest as reduction in energy use and energy replenishment.

Results from many studies, however, have shown that the regulation of autonomic outflow is much more complicated than we thought, and the previous model has ceded place to an organizational model that emphasizes functionally differential controls of sympathetic outflows to specific targets. Investigators propose that the activity-oriented behavior and reflex response are topographically activated by a specific population of sympathetic premotor and motor neurons in the hypothalamus, the midbrain, the medulla, and the spinal cord (49, 75, 76, 84).

The sympathetic premotor neurons (SPNs) located in the rostral ventrolateral medulla (RVLM) are involved in the regulation of the cardiovascular system, which maintains tissue perfusion pressure and nutritive blood flow. Neurons that control the sympathetic vasomotor outflow to muscle are located in lateral and caudal portions of the RVLM; those located more medially concern the activation of cutaneous sympathetic nerves, and the rostromedially located neurons are capable of activating renal, cardiac, and lumbar splanchnic nerves (10, 17, 18, 64, 70).

Even though the mechanisms of differential

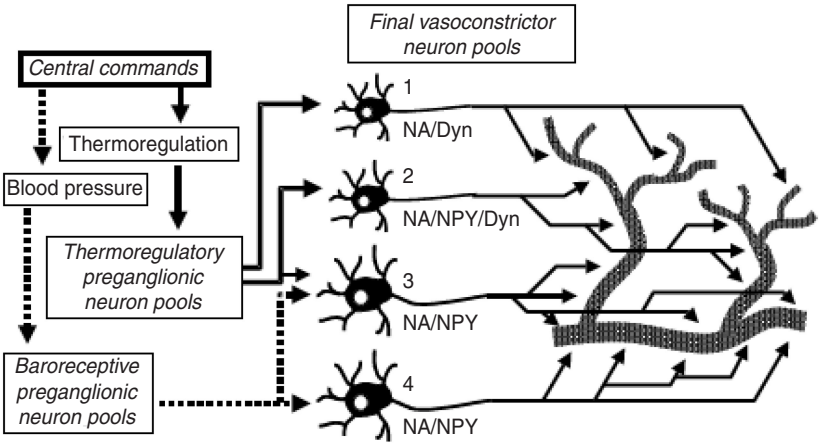

Fig. 1. A proposed model for the 'vasomotor units' derived from the organization of the sympathetic vasoconstrictor neurons innervating the cutaneous vasculatures in guinea-pigs. Four vasoconstrictor neuron pools innervate selectively to consecutive segments of the vascular bed. Final vasomotor neurons in distinct pools are regulated by a specific pool of preganglionic neurons that are under thermoregulatory or baroreceptor controls. The neurons in different pools are all noradrenergic and may express different neuropeptide patterns to activate different functions. NA: norepinephrine; NPY: neuropeptide Y; Dyn: dynorphin. (This figure is reproduced from the reference (24) with permission from the publisher.)

control in distinct sympathetic functions have not yet been investigated thoroughly, it is suggested that most sympathetic functions are processed by an activity-dependent model that is based on the topographic location of the distinct groups of SPNs in the central nervous system.

Sympathetic Function and Blood Flow

As mentioned, the differential control of SNS is evident; another question then arises concerning whether the regional blood flow is also regulated in a functionally specific manner.

The SNS innervates all vasculatures supplying oxygen and nutrients to the vital organs and removing wastes from them. Insofar as SNS immediately responds to internal and external environmental changes, sympathetic activity is crucial for animals' survival. Researchers have extensively studied the organization and responses of the sympathetic outflows to the blood vessels, and have identified an activity-oriented pattern (16, 24).

Functional Organization of Peripheral Vasomotor Pathways

A single vasomotor neuron innervates certain areas of the vasculature; and different functional pools of vasomotor neurons innervate distinct segments of the vasculature, serving the selective and graded neural control in proximal or distal regions of blood vessels (24, 25). Binder and Mendell have concluded that a fundamental structure of somatic motor systems is a variously sized motor unit consisting of a motor neuron and all the muscle fibers that it innervates (5). Given that the autonomic preganglionic neurons share a common embryological origin with somatic motor neurons (83), Gibbins and his coworkers proposed that sympathetic pathways regulating the vasculature are organized into a pattern of 'vasomotor units' or 'neurovascular motor units', which is similar to the pattern of motor units in the somatic nervous system (24). As shown in Fig. 1, each vasomotor unit consists of a preganglionic neuron with the vasomotor neurons it projects, and the blood vessels innervated by the vasomotor neurons (24, 26, 73, 74).

The vasomotor units are organized into distinct functional pools, which can be recruited to provide specific and graded control of blood flow in distinct vascular beds. The activity of the vascular smooth muscle is regulated by the integration of various factors such as the sympathetic vasomotor outflow onto that area, circulating vasoactive agents, factors released from the endothelium, and the smooth muscle itself. Preganglionic neurons can be recruited according to the descending command from the brainstem (27) and the segmental input originated from sensory afferent inputs (31). Graded control of the vascular smooth muscle is achieved by the selective recruitment of the appropriate combination of vasomotor units. As increasing strength of vasomotor output is required, more vasomotor units are recruited instead of there being an increase in the firing rate of individual neurons (36, 65).

Neural Control of the Vasculatures

Autonomic vasomotor pathways operate in re-

sponse to a changing environment, and the blood flow of specific tissue is altered by a variety of physiological or pathophysiological factors consecutively. Vasculatures in distinct tissues receive a certain tonic level of sympathetic control that is under the influence of specific factors. The vascular tonic level of skeletal muscle is primarily under the baroreceptor control; however, thermoregulatory control is the major factor to control the tonic level of cutaneous vasculature except for the proximal, larger vessels, which in turn, are regulated under baroreceptor control (28, 72).

The sympathetic neural activity is primarily involved in the regulation of muscular blood vessels that are influenced by the distinctly functional demand of the distinct vascular segment (66). Compared to the proximal segment, the distal segment of the resistance vessel is more sensitive to the metabolic demands of muscle contraction, and is also better able to override the effects of sympathetic nerve activity (28, 29, 71). During exercise, sympathetic vasoconstriction sustains itself in proximal feeding arteries to protect arterial pressure, while metabolic factors override sympathetic vasoconstriction in distal arterioles to enhance capillary flow (100).

The differential control of blood flow to distinct regions of the body is dependent on the correlated central SPN groups, which are regulated by the specific functional demand of distinct organs rather than by the anatomic location of the body (69). This organizational principle is also supported by the anatomical findings that extensive axonal branching of an individual SPN projects to the ganglionic neurons of the intermediolateral nucleus in multiple thoracic spinal segments, and these neurons are considered to innervate the correlated end-organ tissue (3, 63, 77).

Somatic Stimulation Induces Sympathetic Reflexes Specifically

Many sympathetic preganglionic neurons in the spinal cord participate in controlling the functions of visceral organs and blood vessels. Activation of the somatic afferent evokes both excitatory and inhibitory sympathetic responses in many regions of the body (51). Although research has proved that the mechanism of blood-flow regulation is similar to the specific patterning of SNS in response to certain stimulation, research has yet to elucidate the organization of neural circuits specifically controlling many other sympathetic reactions in response to somatic stimulation.

SSR elicited by inputs from the group III and IV cutaneous and muscular afferents are mediated by both spinal and supraspinal pathways (89, 91, 92). The spinal component is arranged segmentally and is mediated by polysynaptic circuitry in which responses of sympathetic efferents arise from the same spinal cord segment (91, 92). In contrast, the supraspinal component of SSR has a wider response and is mediated by circuitry that includes the RVLM and can be recorded from sympathetic efferents arising from several segments of the spinal cord (2, 68, 78, 89).

Peripheral noxious stimulation, such as skin pinching, evokes an excitation of vasoconstrictor sympathetic outflow in muscles and visceral organs but an inhibition of vasoconstrictor efferent in the skin (41). However, a completely reversed reaction is found in the anesthetized rabbit when the noxious stimulation is applied to the facial skin, which is innervated by the trigeminal nerve. In such a stimulation, the sympathetic outflows in the splanchnic nerve, renal nerve, and skeletal muscle are decreased, but those in cutaneous vessels are increased (57, 111). Results of previous experiments indicated that inhibition of neurons in the medullary raphe selectively inhibits the cutaneous vasoconstriction in the rabbit ear during trigeminal stimulation, whereas inhibition of neurons in RVLM induces an inhibition of the mesenteric vasoconstriction caused by abdominal vagal stimulation (6, 7).

Observations from clinical works have shown that cutaneous vasoconstriction is evoked in anesthetized humans during surgical incision (82, 94). Ischemic injury of the body induces differential reactions involving the suppression of cardiac sympathetic discharge and the enhancement of adrenal epinephrine secretion (110).

Evidence of a more direct nature regarding differential control of SSR was provided by a previous study that investigated the patterning of sympathetic activity that occurs in response to activation of the vestibular labyrinth in the cat (50). Research suggests that vestibulosympathetic reflexes, mediated through brainstem circuits that include the RVLM (109), play a significant role in maintaining blood pressure during postural changes (108). These findings also suggest that vestibular stimulation affects only specific components of the SNS; it does not induce global or nonspecific responses throughout the sympathetic efferents of the body. The relative magnitude of vestibulosympathetic reflexes differs from nerve to nerve; these responses are greater in the renal nerve than in other sympathetic nerves of the neck, abdomen, and pelvis (50).

Findings from another experiment also demonstrate that different types of somatic stimulation elicit specific patterns of sympathetic nerve activation through distinct neural circuits (53). Inputs from skin and muscle elicit a specific patterning of sympathetic response, which is different from that produced by vestibular stimulation. Renal, superior mesenteric, and lumbar colonic nerves respond most strongly to forelimb and hindlimb nerve stimulations, whereas

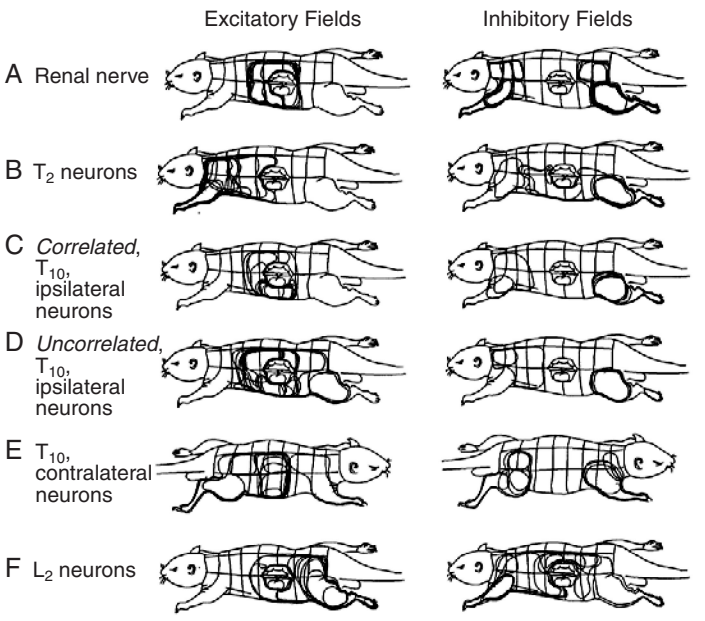

Fig. 2. Cutaneous fields for noxious stimulation that excited (*A*, *left*) and inhibited (*A*, *right*) renal sympathetic nerve activity or excited (*B-F*, *left*) and inhibited (*B-F*, *right*) dorsal horn neurons in the spinal segments indicated. For clarity, only representative fields are illustrated. (Both this figure and its illustration are reproduced from the reference (13) with permission from the publisher.)

external carotid and hypogastric nerves are least sensitive to these nerve stimulations.

An interesting experiment (Fig. 2) involving spinalized rats examined the ongoing and stimulus-evoked activity of sympathetically correlated neurons in the intermediate zone and dorsal horn, and revealed that the same stimulus may differentially affect separate sympathetic efferent pathways of the body, exciting one and inhibiting the other (12, 13). The results show that noxious cutaneous stimulation of the flank around the T10 and the nearby dermatomes simultaneously increases both renal sympathetic activity and the activity of correlated dorsal horn neurons. Noxious stimulation of more rostral and caudal regions of the trunk, such as the shoulder and hip, decreases both renal sympathetic activity and the activity of correlated dorsal horn neurons. Therefore, it is suggested that sympathetically correlated T10 dorsal horn neurons might be excited prior to the preganglionic neurons of the renal sympathetic nerve, which are involved in the generation of ongoing renal sympathetic activity. This evidence also suggests that these dorsal horn neurons might play a role in mediating infraspinal somatosympathetic reflexes after spinal cord transection.

Above-mentioned data have provided evidence that it is possible to define a topographic relationship between the somatic stimulation site and the sympathetic response site, either excitatory or inhibitory. Furthermore, the selected stimulation sites eliciting excitatory sympathetic responses should be different from those for inhibitory sympathetic responses.

Acupuncture, Blood Flow, and SSR

The differential control of sympathetic reflex evoked by somatic stimulation gives rise to a possibility of developing a novel method for manipulating the regional blood flow of certain areas to improve the congested or ischemic conditions associated with certain kinds of pain. Acupuncture and moxibustion are thought to be functioning through somatic stimulation; therefore, their widely used concepts and pertinent clinical experiences may provide valuable data for exploring the mechanisms of SSR.

According to the concept of traditional Chinese medicine, the meridian system is considered to be an elementary basis of acupuncture and moxibustion therapy. However, scientific studies have yet to present clear evidence for meridians, except for the "de-qi" sensation and the phenomenon of sensory propagation along channels (9, 81).

As mentioned above, although there is confirmation that acupuncture analgesia can serve as effective treatment in certain types of pain both clinically and experimentally, the effects of acupuncture analgesia cannot be explained satisfactorily by many proposed mechanisms. In classical Chinese acupuncture, the site of treatment is highly variable depending on the precise location of the pain and on the given therapist's experiences. The effectiveness of pain therapy is sometimes also quite variable even under the same

therapist's experiences: the therapeutic regimen like duration, frequency, and intensity of needle stimulation are not standardized. Therefore, researchers should further study the differential control of SSR, especially acupuncture-induced SSR, to overcome the above-mentioned shortage and to improve the quality and effectiveness of acupuncture therapy.

Acupuncture and the Sympathetic Nervous System

Several lines of studies have provided evidence that both manual acupuncture and electroacupuncture (EA) induce a sympathetic effect. The input signals from sensory afferents lead to a series of central and peripheral neurological effects, and SSR is believed to be induced both segmentally and intersegmentally. During acupuncture stimulation, a localized short-term cooling effect in skin and muscle surrounding the acupoint is noted, suggesting a transient increase in segmental sympathetic activity, and then a long-lasting warming effect is induced, indicating that the sympathetic activity is reduced (21-23, 52, 56, 98). Besides the local effect, TENS evokes a general vasodilatation and a sensation of warmth all over the body (45). Local effects are thought to be induced through segmental somatosympathetic and axon reflexes, whereas the general effect is mediated by a central SSR, which may induce either excitatory or inhibitory sympathetic effects.

The intensity of pain relief, evaluated by means of the visual analogue scale (VAS), has been proved to be correlated to the reduction of sympathetic vasomotor activity (99). Findings regarding an EA in the upper extremity, with 2 Hz maximal tolerated electrical stimulation that creates no discomfort, have shown that EA elevated the dental pain threshold and significantly elevated the sympathetic nerve activity in the muscle that was innervated by the peroneal nerve (22).

The transient increase in skin sympathetic nerve activity (SSNA), accompanied by "manual acupuncture"-induced reduction in skin blood flow, is dependent on the baseline of SSNA (52). Findings reveal that blood pressure is unchanged throughout the period of acupuncture stimulation. Besides the duration of stimulation, the intensity of stimulation may relate to the effects of acupuncture. Several lines of data suggest that strong stimulation tends to increase the sympathetic outflow but that weak stimulation leads to a decrease in the activity (89).

Effects of Acupuncture on Blood Circulation in Skin and Muscle

It has been suggested that acupuncture, by increasing blood flow in local and remote muscles, not only can flush out NSs but also can induce pain relief (42, 54, 55). The contracture and energy crisis mechanism of myofascial pain indicates that the contraction of muscle and ischemia leads to the release of various chemicals that sensitize nociceptors (95, 102). The activation of polymodal receptors on sensory terminals is considered one of the modes of action of acupuncture because these receptors have a relatively low threshold and a wide dynamic response range, and they are easily sensitized by certain chemical substances such as prostaglandins, bradykinin, and histamine (47).

Acupuncture evokes flare (vasodilatation) and wheal (extravasation) responses around the site of stimulation, and these responses stem from antidromic activation of capsaicin-sensitive sensory afferent fibers (48, 90). These findings suggest that local flare and wheal responses induced by acupuncture might, themselves, stem from a release of neuropeptides acting on blood vessels' receptors, the function being to induce an effect like neurogenic inflammation.

Both experimental and clinical studies have shown that acupuncture and related treatments, including TENS, produce peripheral vasodilatation, in skin and muscle, mediated probably by the release of vasoactive neuropeptides, mainly SP and CGRP (42, 46, 55). These results also indicate that the antidromic vasodilation is independent of systemic blood pressure (46). This kind of neuropeptide release, when resulting from acupuncture, is also shown to significantly increase the blood flow in the parotid and submandibular glands (8, 58).

Sandberg and his coworkers have conducted a series of experiments to examine the acupuncture-induced regional blood-flow changes in skin and muscle in both healthy people and subjects with muscle pain. The data have shown that the sympathetic activity of healthy subjects is not the same as the sympathetic activity present in a pathological condition; in other words, the acupuncture-induced blood-flow increase in skin and muscle depends on the stimulation pattern and the subject's condition (85-87). Research has shown that in healthy subjects, a significant increase in skin's or muscle's blood flow accompanies deep muscular needle stimulation, but not subcutaneous needle insertion (87). However, in fibromyalgia patients, a significant increase in blood flow is observable in skin and muscle when the needle is inserted into either deep muscle or subcutaneous tissue in painless regions (85). In comparison with the myalgia patients, the muscle blood-flow increase of deep muscle needle stimulation is significantly larger in healthy subjects. The muscle blood flow corresponding to deep muscle stimulation is positively correlated with the pressure pain threshold in the trapezius muscle, and negatively correlated with spontaneous pain. These findings suggest that the

patterns of muscle blood-flow response to the acupuncture may reflect the condition of increased sympathetic activity and a generalized hypersensitivity in myalgia patients.

Research has observed differential effects both in applications of EA to different areas of the body and in different intensities of stimulation. In anesthetized rats, EA stimulation to the hind paws increases the intensity-dependent arterial pressure and RBC velocity in mesenteric arterioles, while EA stimulation to the back decreases arterial pressure and RBC velocity (80). In anesthetized, artificially ventilated rats, the blood flow in biceps femoris muscle shows differential responses when EA stimulation is applied at intensities of 0.1-10.0 mA and at frequencies of 1-20 Hz to a hind paw (79). The response patterns of muscle blood flow and mean arterial pressure are correlated with the excitation of different groups of muscle afferent by different intensities of EA. Therefore, the investigator has concluded that EA stimulation to a hind paw at an intensity sufficient to excite the group III and IV afferent fibers can decrease muscle blood flow *via* sympathetic reflex, although this blood flow decrease is overridden by an increase in muscle blood flow caused by elevated mean arterial pressure.

The evidence from acupuncture and related techniques has supported the assertion that regional sympathetic activity and blood flow are regulated differentially by distinct conditions that include treatment method, intensity of stimulation, site of stimulation, and the health condition of subjects. Therefore, we speculate that each kind of pain must correspond to a unique treatment, depending on the pain situation and the patient's condition, to achieve better primary effects and less intense side effects.

A Hypothesis That SSR Mediates Some Effects of Acupuncture Analgesia

The most convincing phenomenon concerning Ying and Yang theory is the antagonistic action between flexor and extensor muscle groups of the trunk and extremities. The pathways of the meridian, along the long axis of the trunk and extremities together with muscle groups, are divided into flexor and extensor sides. This anatomic correlation implies that the function of meridian between Ying and Yang might be correlated with the interaction between flexor and extensor muscles. During flexion of the trunk and extremities, the muscles of each flexor muscle group contract simultaneously across the joints, and all related nervous systems activate specifically to meet the functional demand. When the motor neurons activate to contract flexor muscles, the sympathetic activity declines to increase blood flow and the proprioreceptor inputs of the sensory nervous system change in response to the increased muscle tone. The activities of these three nervous systems are reciprocally reversed in the antagonistic extensor side during flexion in which [1] the motor activity decreases to relax the extensor muscles, [2] the sympathetic tone increases to reduce blood flow, and [3] the proprioreceptor inputs change in response to the decreased muscle tone. During the extension that occurs in the same part of the body, all the neural activities, whether in the extensor or the flexor sides of the trunk and extremities, undergo a reversal to the abovementioned condition.

To explain the functional patterning of SSR, we propose here a model of a "neuromeridian functional unit" or "neuromeridian unit". This concept is similar to the concepts of the motor unit, the vasomotor unit, and the spinal autonomic motor program. A neuromeridian unit is composed of a functional pool of sympathetic vasomotor units and the tissues it supplies, and all the components in a neuromeridian unit operate concomitantly to meet the functional demand of specific activity. Clinical observations of pathophysiological phenomena suggest that neuromeridian units are perhaps arranged along the distribution of meridians, which has been an element of human knowledge for at least 3,000 years. According to this suggestion, the tissues both along a meridian and combined with the neighboring tissues are organized and regulated by the same neuromeridian unit group. A somatic stimulation induces SSRs, which recruit different numbers of neuromeridian units in different response sites, and the intensity of SSR depends on the recruiting number of neuromeridian units.

The functional groups of neuromeridian units in flexor side, named as Ying meridian, and extensor side, named as Yang meridians, are antagonistic in either physiological or pathological conditions. The Ying and Yang meridians also reciprocally respond to the same somatic stimulation in an antagonistic manner; in other words, the response of SSR to somatic stimulation is reversed in the corresponding Ying and Yang meridians.

Since stimulation of a given part of the body would enhance or reduce sympathetic activity of other parts of the body specifically, the selected stimulation for pain relief in ischemic conditions should be different from that in congestive conditions, and also different between flexor and extensor sides of the body. Thus, the mechanism underlying the acupuncture analgesia might operate partly through SSR, especially the differential regulation of regional blood flow. Previous experimental and clinical data have shown that somatic stimulation-induced SSR includes [1] local and nearby reactions, [2] distant reactions

along the same meridian, and [3] distant reactions in different meridians. The mechanisms of each type of SSR warrant detailed exploration if research is to develop a method for selectively modulating the regional blood flow by somatic stimulation.

Future Perspectives

Almost all the studies investigating the relationship between acupuncture and blood-flow change are confined to the local and neighboring skin and muscle; little is known about the involvement therein of distant skin or muscle. Because studies have proved that the sensation of propagation can occur through the meridian, and have found that acupuncture relieves pain effectively along the meridian (whether in neighboring or remote areas), future research should explore whether or not neuromeridian units exist and, if they do, what characterizes their organization and functions. Research should satisfactorily define the functional relationships among any distinct neuromeridian units to help develop a more efficient method of pain relief resting on acupuncture-related or TENS-related techniques.

Several concepts of acupuncture treatment that have been proposed and widely applied to the treatment of pain include the internality-externality concept, the upper-lower concept, the right-left concept, and the male-female concept, and all of them can operate consistently in the context of the Ying-Yang principle. Many Chinese clinicians have described many acupuncture principles that rest on clinical experiences and that are difficult to examine by means of those methods used previously. Since the hypothesis of the neuromeridian unit could fill the gap between traditional meridian theory and modern neuroscience, SSR may provide a valuable direction for advanced exploration. Researchers might define a clear topographical relationship between a stimulation site and differential response sites by investigating the mechanisms of SSR in detail.

Conclusion

Research has confirmed that pharmacological intervention, the most popular treatment for pain relief, causes many side effects and that its effectiveness is limited further by impaired blood circulation. Since impaired blood circulation is associated with pain in either neurogenic inflammation or ischemia conditions, improving the blood perfusion to eliminate NSs in local tissue is a feasible method for pain relief.

SNS controls blood circulation, and research treats acupuncture as an effective way to improve impaired blood flow and to relieve pain through the mediation of SSR. Research has suggested that SNS and SSR act according to a differential control manner; hence, researchers should thoroughly explore the SSR mechanism to develop a novel method of pain relief that yields high levels of effectiveness and low levels of side effects.

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