

Original Paper

Acupuncture and Neurophysiology

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ABSTRACT

Application of acupuncture methods goes back centuries. Today, there is much scientific research and many approaches to explain the mechanism of acupuncture. Among these approaches, the most popular one is the neurophysiologic approach. In this paper, we explain the series of events that follow the insertion of acupuncture needles under the headings of local reactions; regional reflexes related with viscerocutaneous and cutaneous-visceral reflexes; increased levels of β -endorphin, enkephalin, and serotonin in the central nervous system and plasma; and effects of these neurotransmitters in the nervous system and many other systems. We then address the clinical application of this neurophysiologic approach.

Key Words: Acupuncture, Neurophysiology, β -Endorphin, Enkephalin, Serotonin, Viscero-Cutaneous, Cutaneous-Visceral Reflex

INTRODUCTION

THE NERVOUS SYSTEM, TOGETHER WITH the endocrine system, provides many of the control functions for the body. It controls activities such as rapidly changing visceral events and the rates of secretion of some endocrine glands. The nervous system receives millions of bits of information from the different sensory organs and then integrates all these to determine responses made by the body.

Acupuncture, as needling therapy, is a kind of specialized sensory stimulation that is analyzed through sensory neural pathways. Many neural theories have been developed to explain the mechanisms of action of acupuncture. Studies have revealed the importance of neurophysiologic research in explaining the effect mechanism of acupuncture. Applying acupuncture shows reactions in local, regional, central nervous system, and general levels:

- **Local Reaction.** Insertion of the acupuncture needle to the acupuncture point creates the first reaction in the region. Following this reaction, a series of events occur in the area.

- **Regional Reaction.** The activation of an area (dermatomes) through reflex arches. Acupuncture's effects stimulate the viscerocutaneous, cutaneous-visceral, and cutaneous-muscular reflexes.
- **Central Nervous System.** The stimulus generated by insertion of the acupuncture needle to the acupuncture point reaches the cortex in the spinal cord and brain stem and activates the pain control system by stimulating the periaqueductal and periventricular neurons in the mesencephalon. Neurotransmitters like β -endorphin, enkephalin, and serotonin are released by activation of the pain control system.
- **General Reaction.** The neurotransmitters elevated in the central nervous system and plasma affect many organs and systems and, most important, the nervous system.

LOCAL REACTION

Most activities of the nervous system are initiated by sensory experience emanating from sensory receptors. In acupuncture, application is made to the skin and subcuta-

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neous muscle tissue, and local effects are observed in these tissues. Most of the acupuncture points are either identical to the trigger points¹ or to the motor points.² Some other acupuncture points are located on superficial nerve divisions or sites with condensed nerve plexuses. These points are rich in the vascular network and closely related to the lymphatic system.^{3,4}

Acupuncture points have low electrical resistance⁵ and high electrical potential compared with ordinary skin points; various types of point detectors have been developed according to this property.⁶ Due to different substance concentration of acupuncture points, they have different electrical charges. When these points are needled, increased calcium concentrations are detected.^{3,4}

Acupuncture points are different in the distribution of the somatosensory receptors and the number of free nerve endings. They are also the dense loci for nociceptors, golgi-tendon receptors, Meissner corpuscles, Krause's end-bulbs, and glomus-bodies.⁷ Insertion of needles to different acupuncture points may stimulate different combinations of these receptors. When a needle is inserted into the Shangyang (LI 1), Zhongchong (PC 9), and Shaoshang (LU 11) points, it stimulates the receptors of touch and pressure, which are 2 sense receptors. When the needle is inserted into the Neiguan (PC 6) and Yuji (LU 10) points, it stimulates the muscle fibers because these points are located deep in tissue, which has many muscle fibers. Accordingly, when a needle is inserted into the Daling (PC 7) point, it stimulates the receptor of the golgi tendon and/or pressure receptors.⁸

When the acupuncture points are needled, this tissue damage will result in secretion of some "endogenous algogenic substances." One of these substances is plasma kininogen, which is the precursor of bradykinin that activates nociceptors. In addition, serotonin is released from the platelets. Serotonin directly activates nociceptors. Serotonin and bradykinin affect the phospholipids at the cell membrane and result in the release of leukotrienes and prostaglandins. Hageman factor (factor XII) secretes with the coagulation system, plasminogen, kinins, and complement system activation. At the stimulation point, mast cells of Lewis layer and cells around the needle secrete bradykinin, histamine-like substances, heparin, adrenocorticotrophic hormone (ACTH), serotonin, and protease. Prostaglandins increase the nociceptor sensitivity and accumulation of more algogenic substances by making vasodilatation. After vasodilatation, local edema, migration of leukocytes, and mast cell secretion of the cytokines tumor necrosis factor- α , interleukin-6 (IL-6), and interleukin-1 (IL-1) stimulate the hypothalamus to secrete corticotropin-releasing hormone (CRH). By a reflex mechanism, neuropeptides are released to the peripheral tissue from the nociceptor endings, which have more sensitivity. Especially tachykinins like substance P and neurokinin A will initiate inflammation and edema in the area.^{9,10} The intracellular potassium is released from the

damaged cells. Potassium has activating character for the nociceptors. The histamine released from the mast cells also activates the nociceptors directly.¹¹ Thus, inflammation occurs in addition to edema and vasodilatation; the condition that is formed due to stimulation of the nociceptors is called neurogenic inflammation.¹²

The inflammation that is produced by insertion of the acupuncture needle to the acupuncture point activates many anti-inflammatory mechanisms like anti-inflammatory cytokines, lymphocyte proliferation, thrombocytosis, release of serotonin, corticosteroid release from the lymphocytes, and endogenous opioid release.

The hypophysis anterior lobe secretes β -endorphin and ACTH as a reaction to insertion of the acupuncture needle. The signals from the skin are first transmitted to the spinal cord and from there, to the brain stem, thalamus, and sensory cortex, and pain control mechanisms are activated as the periaqueductal gray matter in the mesencephalon and periventricular cortical neurons are stimulated. These neurons send their axons to enkephalinergic neurons at the nucleus reticularis paragigantocellularis and nucleus raphe magnus. Enkephalinergic neurons are in contact with cerebral cortex and hypothalamus and the signal transmission at these sites is performed by enkephalin. Hypothalamic neurons secrete endorphin to the synaptic cleft. Thus, the diencephalic endorphin and mesencephalic enkephalin neurons stimulate the serotonin neurons at the bulbus.^{11,13,14} The serotonergic neurons at the dorsal horn of the spinal cord stimulate the intermediate neurons at the dorsal horn. The intermediate neurons at the dorsal horn are called the enkephalinergic neurons and the synaptic transmission of these neurons is done by enkephalin. At these sites, there are many neurons with dinorphine.¹³

β -Endorphin and enkephalin, which play the key role in pain control systems following acupuncture application, have anti-inflammatory effects. β -Endorphin is effective in progression of inflammatory events. In a study of rats,¹⁵ anti- β -endorphin was applied to eliminate the effects of β -endorphin, and inflammatory reactions grew much faster in these animals. Cabot et al found that inflammation increased the concentration of proopiomelanocortin mRNA and increased secretion of β -endorphin in lymphatic cells both related and not related to the inflammation.¹⁶ It is found that in inflammatory events, macrophages and lymphocytes synthesize enkephalins. Methionine enkephalin has a strong anti-inflammatory effect.

Regional Reaction

Many findings report that acupuncture acts at a spinal (segmental or regional) level. Needle stimuli from the periphery lead to release of neurotransmitters in the spinal cord level. These neurotransmitters (tachykinins, substance P, neurokinin A, calcitonin gene-related peptide, somatostatin, enkephalin, etc) modulate the transmission of nociceptive

information to the central nervous system. Visceral functions of the body like arterial blood pressure, pulse, bladder control, sweating, body heat production, digestive secretions and gastrointestinal motility, and metabolic functions are controlled by the autonomic nervous system.¹¹ Acupuncture application for visceral organ diseases is mainly based on the fact that back-Shu and front-Mu points stimulate related segmental autonomic nerves.

Sympathetic nerves take their source from the T-1 and L-3 segments of the spinal cord, first to the sympathetic chain, then to the organs and tissues controlled by the sympathetic nerves. Some preganglionic nerves, which pass through the paravertebral ganglion chain, end at the postganglionic neurons of the collateral ganglions near the visceral organs. From these ganglions, postganglionic axons are distributed to the visceral organs.^{11,13,17,18} The primary parasympathetic neurons are situated at the cranial nervous nucleus and sacral 2 to 4 nuclei.^{11,13}

Two reflexes related to the autonomic nervous system explain the effects of acupuncture on the internal organs. These are viscerocutaneous and cutaneous-visceral reflexes. Viscerocutaneous reflex is sensation of the pain, irritation, and sensitivity related to an internal organ on the related skin area of that organ. Each internal organ and its related skin is innervated by the same segments of the spinal cord. The nociceptive impulses from internal organs pass to the dorsal horn and also to the ventral horn across interneurons. The cutaneous nociceptors use the same pathway and there is substantial mixing of the 2 input sources. Thus, the nociceptive senses from the internal organ converge on the dermatomes related with the segments supplying autonomic innervation to that organ. In medical practice, this concept is known as referred pain. For example, pain in the gallbladder is projected on the skin of the right hypochondrium and on the top part of the right shoulder. A pain related to stomach ulcers may correspond to the 11th thoracic vertebra.

In the cutaneous visceral reflex, irritation of a skin point influences the organ functionally because the cutaneous area is connected to the neurotomes. Somatosensory inputs from the skin and/or muscle are involved in the control of vari-

ous autonomic functions.¹⁹⁻²¹ In acupuncture application, Back-Shu and Front-Mu points are used in the treatment of visceral disease.²² Utilizing acupuncture on the Back-Shu and Front-Mu points awakens the cutaneous-visceral reflexes, and this causes a regulated effect on the organ receiving autonomic innervation from the same segments. Back-Shu and Front-Mu points are important not only in the treatment of diseases of the internal organs, but they also are of clinical significance in the diagnosis of visceral organ disorders. When any of the visceral organs malfunction, positive reactions such as sensitivity or tenderness will be manifested at the corresponding Back-Shu and Front-Mu points (Tables 1, 2; Figure 1). Palpation of sensitive points can be a useful aid to diagnosis. Stimulating techniques such as acupuncture, moxibustion, or massage may be applied to these points to relieve disorders of the corresponding organs.^{22,23}

The primary sympathetic and/or parasympathetic neurons supplying autonomic fibers to the Lung, Pericardium, Heart, Liver, Gallbladder, Spleen, Stomach, and Urinary Bladder correspond to the dermatomes of the Back-Shu, Front-Mu points related to these organs. This demonstrates relationship between the autonomic system and Back-Shu and Front-Mu points. From these data, we believe that acupuncture to Back-Shu and Front-Mu points can regulate the sympathetic and the parasympathetic activities that affect visceral organs.

Central Nervous System

When the pain nociceptors are stimulated, this stimulus is carried to the spinal cord by the myelinated A delta and unmyelinated C nerve fibers. Cell bodies of the A delta and unmyelinated C fibers are located in the dorsal root ganglion. A delta fibers terminate at laminae I. and V. of the dorsal horn, and C fibers terminate at laminae I. and II. neurons. Stimuli coming by both fibers are carried by the spinothalamic, spinoreticular, spinomesencephalic, dorsal colon, and spinohypothalamic tracts to the brain stem and thalamus.^{11,13,24}

TABLE 1. SYMPATHETIC AND PARASYMPATHETIC INNERVATION OF ORGANS, BACK-SHU POINTS

<i>Organ</i>	<i>Back-Shu point</i>	<i>Segments of the autonomic fibers</i>
Lung	BL 13	T 1-4 sympathetic
Pericardium	BL 14	T 1-5 sympathetic
Heart	BL 15	T 1-5 sympathetic
Liver	BL 18	T 8-11 sympathetic
Gallbladder	BL 19	T 8-11 sympathetic
Spleen	BL 20	T 8-11 sympathetic
Stomach	BL 18	T 5-12 sympathetic
Kidney	BL 23	T10-L2 sympathetic
Large intestine	BL 25	T 8-L4 (take branch from at the level of L 4)
Small intestine	BL 27	S 2-4 parasympathetic
Urinary bladder	BL 28	S 2-4 parasympathetic

TABLE 2. SYMPATHETIC AND PARASYMPATHETIC INNERVATION OF ORGANS, FRONT-MU POINTS

<i>Organ</i>	<i>Front-Mu point</i>	<i>Segments of the autonomic fibers</i>
Lung	LU 1	T1-T4 sympathetic
Pericardium	Ren 17	T1-T5 sympathetic
Heart	Ren 14	T1-T5 sympathetic
Liver	LR 14	T8-T11 sympathetic
Gallbladder	BL 24	T8-T11 sympathetic
Spleen	LR 13	T8-T11 sympathetic
Stomach	Ren 12	T5-T12 sympathetic
Kidney	BL 25	T10-L2 sympathetic
Large intestine	ST 25	T8-L2 sympathetic
Small intestine	Ren 4	T8-L2 sympathetic
Urinary bladder	Ren 3	T11-L2 sympathetic S2-S4 parasympathetic

Spinothalamic fibers originating from laminae I. and V. of the dorsal root of the spinal cord decussate, ascend in the anterolateral pathways, and terminate in the contralateral ventral posterolateral nucleus of the thalamus. From here, third-order neurons initiate and terminate at the postcentral gyrus of the cerebral cortex.¹¹ Spinoreticular pathway neurons originate from the dorsal horn of the spinal cord, decussate, and reach the reticular nuclei in the pons and bulbus or give collaterals. The neurons in this pathway terminate in the intralaminar nuclei. From there, the neuronal information is transmitted to parts of the brain like the anterior part of the cingulate gyrus, amygdala, and hypothalamus. Spinomesencephalic pathway neurons originate from the dorsal horn of the spinal cord, decussate, ascend in the anterolateral pathways, and reach the periaqueductal gray matter nuclei. Neurons originating from this region travel to the parabrachial nucleus in the forebrain, amygdala, hypothalamus, and other limbic system structures. Dorsal column neurons are thought to carry the vascular nociception and somatic touch and position sensations to the thalamus.²⁵ Spinothalamic pathway neurons reach the hypothalamus without making synapse in the reticular formation. This is a recently described pathway that transmits emotionally important information from the skin, lips, genitalia, gastrointestinal tract, intracranial blood vessels, tongue, and cornea directly to the hypothalamus.²⁶

The third-order neurons at the reticular area in the brain stem, periaqueductal gray matter nuclei, and ventral posterolateral nuclei of the thalamus transmit the stimuli to the somatic sensory cortex. In the cerebrum, the 1 and 2 sensory areas, frontal lobe, especially 9 and 12 areas, and posterior parietal regions, and the association fibers connecting these parts of the brain are related to pain.¹¹

Pain Control System

The stimuli created by the insertion of the needle to the acupuncture point is first transmitted to the spinal cord, from

there to the brain stem, thalamus, and sensory cortex, and activates the pain control system by stimulating the neurons in the periaqueductal gray matter and periventricular region.^{11,13}

When the enkephalineric neurons at the periaqueductal gray matter of the mesencephalon and periventricular region are stimulated, these neurons transmit these signals to the paragigantocellular reticular nucleus and raphe magnus nucleus. These endorphineric neurons, originated from the hypothalamus, are in communication with the cerebral cortex and hypothalamic neurons. The synaptic neurotransmitter at the paragigantocellular reticular nuclei and raphe magnus nuclei is enkephalin for the enkephalineric neurons and endorphin for the endorphineric neurons. Thus, the diencephalic endorphineric neurons and mesencephalic enkephalineric neurons stimulate the serotonineric neurons at the bulbus.^{11,13,14,27}

When the reticular paragigantocellular and raphe magnus serotonineric neurons of the bulbus are stimulated, they transmit to the dorsal horn of the spinal cord by the dorsal columns. The synaptic transmission of the serotonineric neurons at the dorsal horn is done by serotonin.^{11,13,24} Some noradrenergic neurons derived from the reticular formation nuclei at the brain stem terminate at the dorsal horn and when stimulated, noradrenalin is released to the synaptic cleft at the dorsal horn.²⁴ The serotonineric neurons, terminating at the dorsal horn of the spinal cord, stimulate the enkephalineric neurons at the dorsal horn and the neurotransmitter used is again enkephalin. In this region, there are many neurons carrying dinorphine.¹³

The enkephalins playing a role in the pain control system makes analgesia at the supraspinal level by binding $\mu 1$ receptors and makes analgesia at the spinal level by binding delta receptors. It is found that released enkephalins make presynaptic and postsynaptic inhibition at the synaptic sites of A delta and C fibers at the dorsal horn.^{13,27} β -endorphin binds the $\mu 1$ receptors at the periaqueductal gray matter, raphe magnus, locus ceruleus, and medial thalamus, and plays a role in supraspinal analgesia.^{28,15} Stimulation of the serotonineric neurons releases serotonin at the dorsal horn synaptic cleft and creates an analgesic effect.²⁹ Serotonin causes adenosine release from the spinal cord and its antinociceptive effect can be antagonized by an adenosine receptor antagonist, 8-phenyl teofilin.³⁰ Endogenous adenosineric system contributes to the antinociceptive effects of opioids, serotonin, and noradrenaline. Stimulation of the pain control system causes noradrenalinergic neurons of the reticular formation to release noradrenalin at the dorsal horn of the spinal cord and creates analgesia by its inhibitory effect on the α -adrenergic receptors.^{24, 31-33}

Chiang et al³² and Takeshige et al³³ found that stimulation of a muscle under an acupuncture point by low-frequency current that can cause contraction creates analgesia; conversely, stimulation of a muscle with the same current under a nonacupuncture point does not create analgesia. It is observed that hypophysectomy and injection of BE antibody into the third ventricle eliminates acupuncture analge-

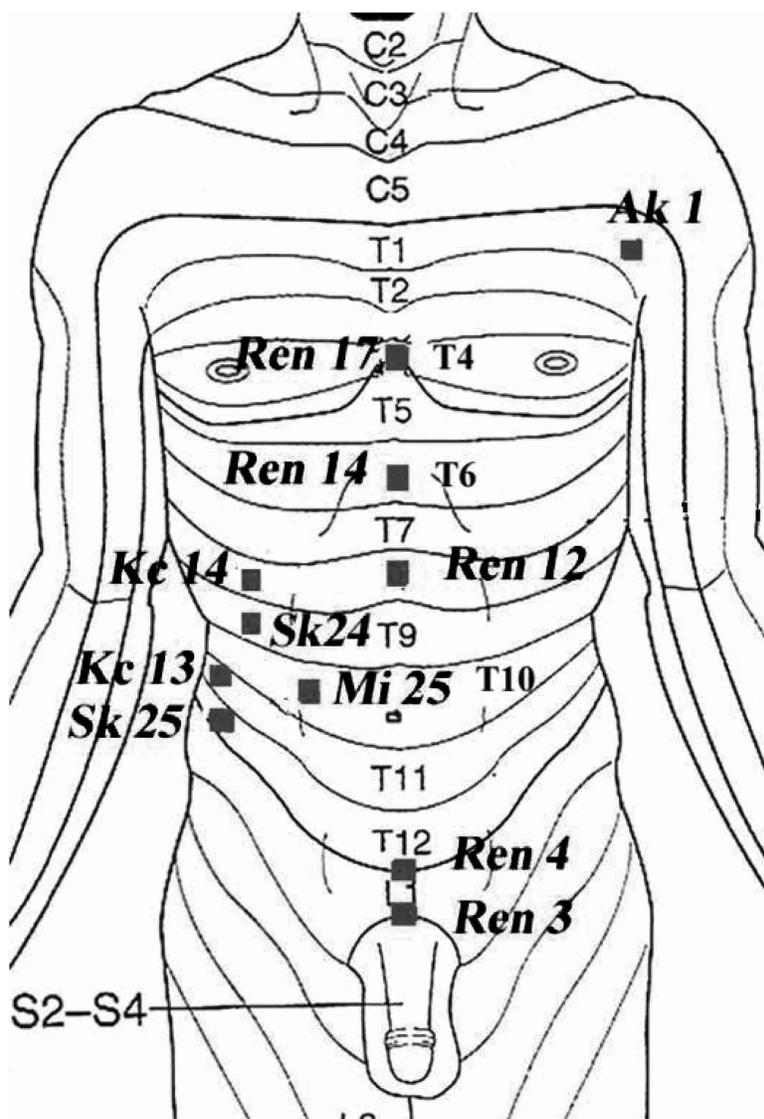


FIG. 1. Dermatomes viewed from the anterior aspect and the corresponding acupuncture points.

sia.³⁴ Electroacupuncture (EA) application induces β -endorphin release from the hypophysis and β -endorphin concentration is increased in the plasma and the central nervous system.^{35,36} Electroacupuncture analgesia is eliminated with the naloxone application and hypophysectomy.³⁴ Acupuncture increases the methionine enkephalin concentration in the cerebrospinal fluid.³⁸ In a study with rats, lateral reticular paragigantocellular nucleus lesions inhibited acupuncture analgesia; conversely, electrical stimulation of lateral reticular paragigantocellular nucleus increased the analgesic effect of acupuncture.³⁹ Acupuncture application also increases the serotonin levels in the central nervous system.⁴⁰ It has been shown that EA creates analgesia by using serotonin 5-HT(1A) ve 5-HT(3) receptors.⁴¹

The stimuli generated by the insertion of an acupuncture needle to the acupuncture point reaches the cortex, and stim-

ulation of the mesencephalic periaqueductal gray matter and periventricular neurons activates the pain control system. Activating the pain control system increases the concentration of β -endorphin, enkephalin, serotonin, and norepinephrine levels in the brain tissue and plasma, thus creating analgesic and many other effects.

General Reaction

Acupuncture application is reported to affect the nervous system,^{34,42,43} metabolism,^{57,44} immune system,^{45,46} gastrointestinal system,^{47,48} and motor functions.⁴⁹

As the mechanism explained in the previous sections, it has been determined that endomorphin-1, β -endorphin, enkephalin, and serotonin levels increase in plasma and brain tissue through acupuncture application.^{40,50} In other reports,

it has also been observed that low-current frequency (2 Hz) EA application increases the concentration of endomorphins, enkephalins, and β -endorphin,^{37,50} but high-current frequency (100 Hz) EA application increased the concentration of dynorphin in the central nervous system and plasma.⁵¹

Serotonin has been implicated in the control of eating behaviors, body weight, and emotions. It is known that serotonin induces happiness, helps a person to feel good, controls sexual motivation, and has a role in obtaining the psychomotor balance. It is presumed that the norepinephrine and serotonin systems normally provide drive to the limbic system to increase a person's sense of well-being. In favor of this concept is the fact that the pleasure and reward centers of the hypothalamus and surrounding areas receive large numbers of nerve endings from the noradrenergic and serotonergic systems.¹³

It has been reported that increased concentrations of plasma and central nervous system concentrations of endogenous opioids bind to the membrane receptors of the nociceptors and create analgesic effect.⁵² Presence of opiate, GABA, bradykinin, histamine, serotonin, and capsaicin receptors on the nociceptor surface membranes indicates that pain suppression level descends from dorsal horn to nociceptor level.⁵³

β -Endorphin affects the development of inflammatory processes. In a study with rats, application of anti- β -endorphin antibodies eliminated the effect of β -endorphin and this accelerated the inflammatory reaction. Richter et al⁵⁴ investigated the lipolytic activity of endorphin in the isolated fat cells of rabbits in vivo. It was determined that as a result of the effect of β -endorphin on fat cells, the levels of free fatty acid and glycerol increased in the rabbit plasma. This effect was blocked by naloxone. Vettor et al studied the lipolytic activity of beta endorphin in isolated human fat tissue.⁵⁵ Enkephalin has antidepressive, anticonvulsive, and anxiolytic effects.⁵⁶

In obese individuals, application of EA at 2-Hz frequency causes weight loss, decrease in the serum leptin levels, and increase in the serum β -endorphin levels.⁵⁰ Electroacupuncture also increases the serum insulin and C-peptide levels and decreases the glucose levels in obese individuals.⁶⁰ Electroacupuncture increases the β -endorphin levels and pancreatic beta cell insulin release in normal rats and rats with type 2 diabetes.⁵⁷ Application of EA at 2 Hz can decrease serum total cholesterol, triglyceride, and LDL cholesterol levels⁴⁴ and increase β -endorphin levels⁵⁰ in obese women. This lipolytic effect of EA may also reduce the morbidity of obesity by mobilizing the energy stores that result in weight reduction.⁴⁴

It has been determined that β -endorphin, met-enkephalin, and leu-enkephalin increase the activity of natural killer cells, the generation of cytotoxic T lymphocytes, the chemotaxis of monocytes, and the production of interferon gamma, interleukin-1, interleukin-2, interleukin-4, and interleukin-6. In the studies on this subject,^{58,59} the conclusions are that

endogen opioids create an immunomodulatory effect. The immunomodulatory effect of acupuncture application was connected with the increase in levels of endogen opioids and serotonin with acupuncture application.⁶⁰

CONCLUSIONS

An increase at levels of β -endorphin, met-enkephalin, leu-enkephalin, and serotonin has been observed with acupuncture. These neurotransmitters have immunomodulatory effects on the immune system.⁶⁰ For all of these above effects, acupuncture can be applied for immune-related diseases, risks of infection, and tissue repair.

Increased levels of neurotransmitters in the plasma and the central nervous system in many clinical applications have indicated that acupuncture has an effect on the nervous system. The local, regional, and systemic neurophysiologic effects described are the main mechanism of acupuncture

DISCLOSURE STATEMENT

No competing financial interest exists.

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