

A brief overview of the analgesic and immunologic effects of acupuncture in domestic animals

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Acupuncture and other complementary and alternative medical modalities are receiving a great deal of attention in the veterinary and human medical fields. Important advances have been made toward the elucidation of mechanisms of acupuncture, with the release of opioids being well-studied. In 1992, an Office of Alternative Medicine (OAM) was established at the National Institutes of Health by congressional mandate. In their 1997 consensus statement, the National Institutes of Health OAM stated that there is sufficient evidence of the value of acupuncture to expand its use into conventional medicine and to encourage further studies of its physiologic characteristics and clinical value.¹ Acupuncture is an ancient form of health care, and the paradigms that supported the origin and development of this modality may seem strange to those who may be unfamiliar with the subject. Indeed, there are many approaches to understanding and using acupuncture, and there are scientifically explainable mechanisms of many of its effects. The intent of our report is to briefly summarize some of the major mechanisms of acupuncture, using explanations that are based on its neurophysiologic, bioelectric, and humoral effects, while recognizing that this form of medicine was derived from conceptual notions of the body that were far removed from our understanding of the body today.

What is Acupuncture?

Acupuncture is an ancient form of diagnosing, treating, and preventing disease that recognizes and encourages the body's own healing potential. It involves the insertion of needles, or other forms of stimulation, into acupuncture points that are precisely defined loci just beneath the surface of the body. There are many ways to stimulate an acupuncture point such as dry needling, injection of fluid into the point, low-intensity or cold laser stimulation, and manual pressure on the point (acupressure). The effects of stimulating these points may be intensified or the duration lengthened by heating or electrically stimulating the needles. The effects of acupuncture may be prolonged by injection of fluid (eg, physiologic saline [0.9% NaCl] solution or vitamin B₁₂) or implantation of gold beads into the point. There are several hundred recognized acupuncture points that are primarily located along acupuncture meridians, or channels, each of which have specific locations and functions.² In practice, however, an acupuncturist's repertoire of points may only include a fraction of these. Characteristics of

acupuncture points and of the tissues between them allow for complete body transmission and integration of bioelectric, humoral, and nervous information.

Approaches to Understanding Acupuncture

There are many approaches that one may take to understand, explain, and use this ancient form of health care, from a Traditional Chinese Medical (TCM) standpoint to a strictly neurophysiologic explanation. Although it is unclear as to where and when acupuncture first developed, practical information regarding its use and application was formalized and recorded early in China. Theories of TCM derive from *Nei Jing (The Yellow Emperor's Classic of Internal Medicine)*, which is the classic Chinese text on medicine and acupuncture believed to have been written during the Warring States period (403 through 221 BC). Principles of treatment, using acupuncture and herbal medicine on animals, were published in *Si Mu An Ji Ji (A Collection of Ways to Relieve Suffering Horses)* during the Tang Dynasty (618 through 907 AD). Another influential work, *Yuan Heng Liao Ma Ji (Treatise on Horses)*, was published and widely distributed in approximately 1608.³ Traditional Chinese medicine dates to ancient times and is based on an understanding of the body that invokes ideas about the environment through which the body moves and lives. The notion of the body as a microcosm within a macrocosm allows for the patient's environment to be taken into consideration with respect to treatment and diagnosis of disease. These theories are still useful today as the classically trained acupuncturist chooses points and herbal medicines, but they may be viewed as untenable in the scientific community.

There are many definable consequences of acupuncture that can be described in neurophysiologic terms. However, the combination of points that a traditionally trained acupuncturist might choose (and the reasons for which they are chosen) will have effects on the body that are more difficult to explain in such a way. There is an abundance of research regarding acupuncture and other forms of complementary and alternative medicine in the international literature. Interest of the United States federal government is evidenced by the holdings at the National Library of Medicine that had more than 60,000 citations on alternative and complementary medicine in 1996.⁴

Morphologic Characteristics of Acupuncture Points and Meridians

Acupuncture points are defined loci just beneath the surface of the body, most of which lie on meridians or channels. Many meridians follow the pathways of

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major nerves, vessels, and fascial cleavage planes. The morphologic characteristics of acupuncture points have been studied grossly, histologically, and electrically. Although there are several types of acupuncture points, not all of which have been studied in detail, the classic point is characterized as a locus just beneath the skin that contains a neurovascular and lymphatic bundle consisting of a connective tissue sleeve that climbs toward the surface of the body, traversing the dermal and hypodermal depths.^{2,5-7} A crucial characteristic of most points and meridians is that they are areas of decreased electrical resistance and increased conductance.^{6,8-10} Although the measurements of electrical conductance have been made from the surface of the body, they are indicative of the electrical properties of tissues just beneath the surface, where points and meridians are thought to lie. It is thought that much of the bioelectric energy that flows so readily through points and meridians are actually passing through the conductive connective tissue sleeve through which the neurovascular, lymphatic, and tendinomuscular structures pass. Collagen, the main component of connective tissue through which the meridians course, has properties that link biologic tissues and physics, namely piezoelectricity.¹¹ Piezoelectricity is the property of a material that results in polarization of the material when subjected to mechanical strain and a change in conformation when subjected to an electric field. Therefore, the effects of needling (a mechanical strain and an ionizing impetus) would include polarization of the surrounding tissue and a change in the bioelectric environment of points and channels that, as stated previously, are preferential pathways of electrical flow. Further, electroacupuncture causes changes in the morphologic characteristics and alignment of collagen fibers, an effect that can be appreciated histologically.⁷ There are important implications to orthopedic and soft-tissue disease states if collagen is considered as a bioelectric mediator of healing and repair. Finally, there are factors that may change or obstruct flow of energy through these channels such as surgical trauma, biological and environmental factors, disease states, and myofascial constrictions.⁶ Acupuncture points can be seen as portals of entry to a conduction superhighway, linking the external to the internal and integrating whole-body humoral, bioelectric, and neural signals.

Acupuncture points may be categorized in many ways (eg, according to their relationship with known neural and tendinomuscular structures). One such scheme separates acupuncture points into 4 categories.¹² Type-I points correspond with motor points. Motor points are known anatomic sites that are located near the point at which a nerve enters a muscle and are defined as those points that induce maximal contraction of the muscle with minimal electrical stimulation. Type-II points are located on superficial nerves in the sagittal plane on the dorsal and ventral midline. Type-III points are found at foci with high densities of superficial nerves and nerve plexi. Type-IV points are located at the Golgi tendon organ, where tendons join muscles. Additionally, many points (approx 70%) coincide with known myofascial trigger points spatially and with respect to their patterns of pain and analgesia

induced when stimulated.¹³ Trigger points are hyperirritable tender regions in muscle tissue that can be palpated as taut bands. These points are similar to acupuncture points for pain in that they may lie within areas of referred pain or may be located at a distance from them, and when stimulated, they can provide long-lasting analgesia.¹³ The close correlation between acupuncture points for pain and myofascial trigger points suggests similar underlying mechanisms of analgesia.

Analgesia Induced by Acupuncture

The effects of acupuncture on the central and peripheral nervous system include activation of the body's endogenous pain modulatory systems, causing a release of serotonin, opioid substances, and other neurotransmitters, thereby altering nociceptive processing and perception.^{14,15} Although, in western medicine, acupuncture is most widely recognized for its analgesic and musculoskeletal effects, signals generated from stimulation of acupuncture points can also affect the viscera, the immune system, and more. How these signals enter the nervous system as a result of acupuncture has been well-researched, with several proposed mechanisms. It is likely that a combination of all mechanisms is responsible for that which is observed clinically.

Researchers have provided evidence based on results of **functional magnetic resonance imaging (fMRI)** that stimulation of acupuncture points causes quantifiable changes in specific regions of the human brain.¹⁵ Functional MRI studies reveal that needle stimulation of a particular point on either side of the body causes activation of structures of the descending antinociceptive pathways and causes deactivation of multiple limbic areas subserving pain perception. These changes were interpreted as activation of the hypothalamus and nucleus accumbens and deactivation of the rostral part of the anterior cingulate cortex, amygdala formation, and hippocampal complex in all persons who experienced acupuncture sensation (a feeling of warmth and heaviness at the point when the needle is appropriately inserted). Further, superficial tactile stimulation (rather than true stimulation of the acupuncture point) induced signal increases in the somatosensory cortex as expected but did not induce decreases in deeper structures, as was observed with true stimulation of the acupuncture point.¹⁵ These observations, coupled with results of fMRI studies in which brain function was localized, suggest that stimulation of acupuncture points can initiate multiple endogenous pathways of analgesia by neuromodulation and integration of neurotransmitter and pain modulation systems at various levels of the CNS.

Endogenous Opioids and Acupuncture

In 1976, shortly after opiate receptors were discovered in the periaqueductal gray matter, the limbic system, and the periventricular gray matter of the CNS, it was demonstrated that acupuncture analgesia could be reversed by naloxone, a pure antagonist at all known opioid receptors.¹⁶ This led to the first awareness that acupuncture analgesia was likely mediated through a system of endogenous opioids.

Nociceptive information is transmitted in the CNS by neurotransmitters. It has been reported that acupuncture induces changes in concentrations of neurotransmitters in the CSF such as serotonin and biogenic amines.¹⁴ Although several neurotransmitters are involved in the transmission, inhibition, and perception of nociceptive information, the opioid peptides met-enkephalin, leu-enkephalin, β -endorphin, and dynorphin have been the most thoroughly studied with regard to the observed systemic and analgesic effects of acupuncture. These opioid peptides are involved in activation of descending tracts that inhibit transmission of nociceptive information in the spinal cord.¹⁷ There is also inhibition of ascending tracts that transmit nociceptive information. When large unmyelinated A- δ fibers (which transmit touch and pressure sensation) are stimulated by the insertion of an acupuncture needle, impulses from small unmyelinated C-fibers (which transmit ascending nociceptive information) are blocked by a gate of inhibitory interneurons in the substantia gelatinosa of the spinal cord, which release neurotransmitters such as γ -aminobutyric acid and enkephalins.¹⁸ There is a resulting inhibition of transmission of pain impulses to the brain for conscious perception. There is also a regional effect, because the A- δ fibers transmit cranially and caudally in the dorsolateral funiculus before entering the substantia gelatinosa to stimulate inhibitory interneurons.^{17,18}

Several different lines of basic research have revealed that some of the effects of acupuncture are at least partially mediated by substances with opiate-like activity and are briefly summarized as follows. Substances known to block opioid biosynthesis (eg, cyclohexamide) or action (eg, naloxone) decrease acupuncture analgesia, whereas peptidase inhibitors such as D-amino acids (eg, D-phenylalanine) can potentiate and prolong acupuncture analgesia, presumably by inhibiting degradation of the analgesic opioid peptides.^{14,16} Opioid concentrations increase in blood and CSF and decrease in specific brain regions during acupuncture analgesia.¹⁴ Mice deficient in opioid receptors had poor responses to acupuncture analgesia.¹⁹ In sum, part of the analgesia induced by acupuncture involves the activation of a neurohumoral system, resulting in the release of endogenous substances with opioid analgesic activity.^{20,21} Administration of naloxone does not decrease baseline thresholds for pain, indicating that the analgesic effects observed are attributable to acupuncture alone.²¹ There is a differential release of β -endorphin, met-enkephalin, and dynorphin in response to low- and high-frequency electroacupuncture.²² Electroacupuncture involves the application of electricity to the needles during stimulation of a point. Different opioid receptors mediate the analgesia induced by low- and high-frequency acupuncture.^{14,17,22,23} The clinical significance of this differential release is that low-frequency electroacupuncture (2 to 15 Hz), which causes the release of β -endorphin and met-enkephalin in the brain and dynorphin in the spinal cord, appears to alleviate deep and chronic signs of pain more effectively than does higher frequency stimulation (100 Hz), which causes release of

dynorphin. Also, the effects of acupuncture in the periaqueductal gray matter may be predominantly mediated by the enkephalins and β -endorphin, whereas effects in the spinal cord are predominantly dependant on enkephalins and dynorphin.²³ Overall, it is likely that the 3 types of opioids act synergistically as they preferentially bind their receptors; β -endorphin and met-enkephalin bind μ and δ receptors, whereas dynorphin is a relatively specific κ agonist.²² Because acupuncture analgesia can largely be blocked by antagonists of any of these receptors, or with the removal or blockage of any of these opioids, it is likely that the various receptors have a synergistic relationship with respect to conferring analgesia when they are simultaneously stimulated by acupuncture.

Effects of Acupuncture on Blood Flow and the Autonomic Nervous System

Acupuncture stimulation activates the central and local autonomic nervous system. On stimulation of an acupuncture point, erythema and heat develop around the needle. In fact, one of the most commonly reported effects of stimulation of an acupuncture point is an increase in skin temperature and a feeling of warmth.² Thermographic studies have identified areas of chronic pain as cold spots and acute pain as warm spots.²⁴ There appears to be a correlation between the effectiveness of acupuncture in alleviating chronic pain and increasing surface temperature. Importantly, unilateral stimulation of certain acupuncture points can cause rapid and long-lasting increases in cutaneous skin temperature bilaterally.²⁴ This suggests that the mechanisms leading to the vasomotor and analgesic effects of acupuncture are at least partially centrally mediated. Increased cholinergic efferent impulses, local vasodilatory factors, and decreased sympathetic tone may all be factors that contribute to this phenomenon.²⁴

Afferent impulses from the myotome of the paravertebral muscle into which an acupuncture needle is inserted ascend to the contralateral anterior hypothalamus to activate a somato-autonomic reflex. Efferent impulses from the cholinergic vasodilator nerves originate from this center and descend to the needled myotome to dilate blood vessels in that region.¹⁷ Vasodilation in the region of the needle is probably also mediated by the physical irritation of the needle placement, leading to release of histamines and other vasodilatory factors. In addition to efferent cholinergic stimulation, there may also be activation of the central sympathetic inhibitory system.²⁴ It has been suggested that acupuncture stimulates muscular afferent nerves at a low intensity level, which causes a pressor response leading to decreased sympathetic tone. This decrease in sympathetic tone may be partially responsible for the bilateral analgesic effects of acupuncture, because cutaneous pain thresholds increase in the blocked and contralateral extremities.²⁵

Acupuncture may affect the pituitary gland via the hypothalamus, causing release of β -endorphins into the circulation.^{6,16} It is unlikely that opioids in the periphery are analgesically active, because plasma concentrations of opioids do not appear to correlate with pain attenuation during acupuncture.¹⁴ It is likely,

however, that opioids in the periphery do have effects on nonanalgesic systems such as immunity.

Changes in the Immune System

Just as stimulation of acupuncture points affect changes in the patient's neurophysiologic and musculoskeletal patterns, it also has profound effects on the immune system. Extensive research on the effects of opioid peptides on the immune system, coupled with research that reveals these endogenous opioids are released into the circulation with acupuncture, provides some clues as to how the immune system can be profoundly altered by acupuncture stimulation.^{20,26} It is likely that acupuncture causes neuroendocrine modulation of the hypothalamic-pituitary axis. Opioids that are released into the circulation from the pituitary gland may interact with cells of the immune system and, therefore, may modulate their function. The interaction of opioids and the immune system is briefly summarized as follows. Normal lymphocytes have receptors for morphine and met-enkephalin.²⁶⁻²⁸ Studies performed in vitro revealed that increased concentrations of met-enkephalin cause an increase in the formation of T-cell rosettes, and this effect is inhibited by the specific opioid antagonist naloxone.²⁷ Natural cytotoxicity was considerably increased with increasing concentrations of β -endorphin and met-enkephalin. The magnitude of enhancement was significantly correlated with increasing concentrations of β -endorphins.²⁹ Studies performed in vivo also suggest that endogenous opioids can modulate immune function.^{26,30} The concentration of β -endorphin in mononuclear cells increases with repeated acupuncture treatments, as does proliferation of T lymphocytes.³⁰ These endogenous opioids also appear to stimulate recruitment of prenatural killer cells and enhance the recycling capacity of natural killer cells; this effect can be blocked by naloxone.²⁹ Acupuncture treatment during phases of acute inflammation may alter concentrations of inflammatory mediators, may alter the ability of WBC to respond to inflammatory mediators, and may have effects on endothelial cells and exudation of plasma.³¹ Therefore, the release of opioids may explain the increases observed in WBC counts, cell-mediated immunity (as measured by T-cell rosette formation or lymphocyte transformation), and enhanced phagocytic activity during acupuncture.^{20,31}

Some of the effects of opioids on immune function appear to involve prostaglandins and interleukin-2.²⁰ Interleukin-2 controls lymphocyte proliferation and natural cytotoxicity; β -endorphin potentiates this process, most likely by blocking an inhibitor of the reaction such as prostaglandin E₂.²⁰ Aberrant prostaglandin production is often involved with aberrancies in immune function. If acupuncture promotes homeostasis with regard to prostaglandin production, then it is understandable why patients with immune disorders may benefit from acupuncture.

The role of opioids in immune system function is multifaceted. Presently, opioids are considered to be communicators between the CNS and the immune system, in part because receptors for these peptides are

found on neurons and lymphocytes. Although much of the research into acupuncture has focused on analgesia, this modality clearly has other uses, partly because of the fact that opioids have widespread effects throughout the body.

Although endogenous opioids play a major role in the observed effects of this modality, there is likely a long list of other influences that are not yet fully understood. Just as there are complex mechanisms involved in the body's own analgesic and immune systems, the use of acupuncture results in a complex interplay among various nervous, bioelectric, and humoral factors.

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