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Acupuncture's Cardiovascular Actions: A Mechanistic Perspective

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ABSTRACT

Over the last several decades, there has been an explosion of articles on acupuncture, including studies that have begun to explore mechanisms underlying its analgesic and cardiovascular actions. Modulation of cardiovascular function is most effective during manual and low-frequency, low-intensity electroacupuncture (EA) at a select set of acupoints situated along meridians located over deep somatic nerves on the upper and lower extremities. Stimulation at these acupoints activates underlying sensory neural pathways that project to a number of regions in the central nervous system (CNS) that ultimately regulate autonomic outflow and hence cardiovascular function. A long-loop pathway involving the hypothalamus, midbrain, and medulla underlies EA modulation of reflex increases in blood pressure (BP). Actions of excitatory and inhibitory neurotransmitters in the supraspinal CNS underlie processing of the somatic input and adjustment of autonomic outflow during EA. Acupuncture also decreases elevated blood pressure through actions in the thoracic spinal cord. Reflexes that lower BP likewise are modulated by EA through its actions on sympathetic and parasympathetic nuclei in the medulla. The autonomic influence of acupuncture is slow in onset but prolonged in duration, typically lasting beyond the period of stimulation. Clinical studies suggest that acupuncture can be used to treat cardiac diseases, such as myocardial ischemia and hypertension, associated with overactivity of the sympathetic nervous system.

Key Words: Autonomic Nervous System, Integrative Physiology, Somatic Afferents, Blood Pressure, Sympathetic Nervous System, Parasympathetic Nervous System

INTRODUCTION

THE PRACTICE OF ACUPUNCTURE began 2000–3000 years ago. Until the last 50 years, acupuncture developed empirically and its art was passed on from teacher to student through practical application. More recently, practitioners began to find that acupuncture had a rightful place in mainstream medicine and could be used to treat a number of conditions and symptoms. The public outside the Orient has accepted acupuncture because of a perception that it reduces pain effectively and successfully reverses a number of other medical problems. Western medical and scientific communities have been more reluctant to accept this practice because of the absence of controlled clinical trials and scant scientific evidence for its mechanisms of action. However, there may be reason for this skepticism to change. The number of articles published on acupuncture research (451 articles worldwide in 2009) has been increasing almost exponentially over the last several decades, with the United States and China both taking lead roles in advancing

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understanding of this ancient therapy.[1] With mounting evidence that acupuncture can be used to treat a number of clinical conditions, including cardiovascular dysfunctions, such as hypertension and hypotension, the rationale for achieving a better understanding of the actions of acupuncture at organ system, cellular, and subcellular levels has become more compelling.[2] This article is a review of recent experimental studies exploring mechanisms underlying the cardiovascular actions of acupuncture, a focus of the laboratory of the Samueli Center for Integrative Medicine and Department of Medicine, University of California, Irvine, over the last decade and a half.

EARLY STUDIES: BEGINNINGS OF A NEW ERA IN ACUPUNCTURE RESEARCH

Two pioneers who used accepted Western approaches to study the mechanisms of actions of acupuncture were Drs. Ji-Sheng Han (PhD) at Beijing University and Peng Li (MD) at Shanghai Medical University. Dr. Han focused on pain while Dr. Li, together with Dr. Tai Yao, (MD) studied acupuncture's action on cardiovascular function. Both researchers described the importance of the central nervous system (CNS) in mediating acupuncture's physiological actions. These researchers found that the endogenous opioid system in the CNS was responsible for much of acupuncture's modulation of pain and hypertension.[3,4] Small studies of patients with coronary disease in the late 1980s and early 1990s suggested that acupuncture reduces electrocardiographic evidence of myocardial ischemia and increases angina threshold.[4–6] In the mid 1990s, I began a long-term collaboration with Dr. Li, exploring peripheral and central neural mechanisms underlying the actions of electroacupuncture (EA) on cardiovascular function. The collaboration involved studying experimental models of myocardial ischemia, reflex-induced hypertension, and, more recently, reflex hypotension. Each model was based on the observation that acupuncture's cardiovascular actions are most prominent when autonomic outflow is stimulated, for example, during visceral sympathoexcitatory reflexes. These investigations over the last 16 years have been reported in a series of more than 30 studies using combined whole animal or human physiological, electrophysiological, anatomical, pharmacological, and, more recently, molecular approaches.

ACUPUNCTURE IN DEMAND-INDUCED MYOCARDIAL ISCHEMIA

Early studies originating from Europe have suggested that acupuncture reduces ischemia in patients with symptomatic coronary artery disease.[5–9] To explore the mechanisms underlying this clinical effect, Dr. Li and I developed a feline model of demand-induced myocardial ischemia, in which the left anterior descending (LAD) coronary artery was ligated, partially allowing normal coronary blood flow at rest but causing an insufficient flow, and hence transient ischemia, identified by the regional myocardial dysfunction, during reflex stimulation evoked by applying bradykinin to the gallbladder.[9,10] This model simulates the most common form of cardiac ischemia experienced during stress by patients with symptomatic coronary atherosclerosis. Thirty minutes of median nerve stimulation with low-frequency, low-current (5 Hz, 4 mA) or, alternatively, percutaneous EA at the PC 5 and PC 6 acupoints (*Jianshi* and *Neiguan* along the Pericardium meridian on the volar surface of the wrist (Fig. 1), using similar stimulus parameters (2 Hz, 4 mA), abolished the stress-induced ischemia.[11] EA reversed the ischemia by blunting the reflex-related increase in blood pressure (BP) significantly but not by increasing LAD blood flow, as measured with a pulsed Doppler flowmeter. A follow-up study showing that acupuncture's action on ischemia could be reversed with intravenous (I.V.) naloxone implicated the endogenous opioid system as an underlying neurotransmitter mechanism (Fig. 2).[12] The site of opioid action during EA was not determined. Given that acupuncture's anti-ischemic effect was noted to be predominately through its BP-lowering effect, subsequent studies have focused on this hemodynamic action of acupuncture. Because percutaneous EA mimicked direct nerve stimulation, it was concluded that the peripheral nervous system and CNS were involved in the EA-cardiovascular response.

OPIOIDS IN THE MEDULLA PROCESS SOMATIC SENSORY INPUT DURING EA

The rostral ventrolateral medulla (rVLM) is a significant source of premotor sympathetic neurons and hence constitutes an important brainstem region that processes somatic and visceral sensory nerve input capable of adjusting sympathetic outflow and, ultimately, cardiovascular function.[13–16] Early investigations from several laboratories suggested that opioids, γ-aminobutyric acid (GABA) and serotonin (5-hydroxytryptamine, 5-HT), might participate in acupuncture regulation of BP.[4,17,18] Recent immunohistochemical studies revealed EA-induced *c-Fos* nuclear expression (a marker of neuronal activation) in the rVLM. These EA-activated neurons contain enkephalin, while β-endorphin is present in closely located axons.[19,20] Both neurotransmitters thus have the potential to participate in processing sympathetic outflow during EA. Pharmacological studies investigating the roles of μ-, δ-, and κ-opioid receptors indicate that β-endorphin (and possibly endomorphin) and enkephalins, but not dynorphin, are involved in rVLM modulation of hypertensive responses during EA.[21] The rVLM and possibly the nucleus raphé palladus (NRP) are the source of enkephalins for the rVLM, while β-endorphin originates in the arcuate nucleus of the hypothalamus.[19,20,22] Visceral

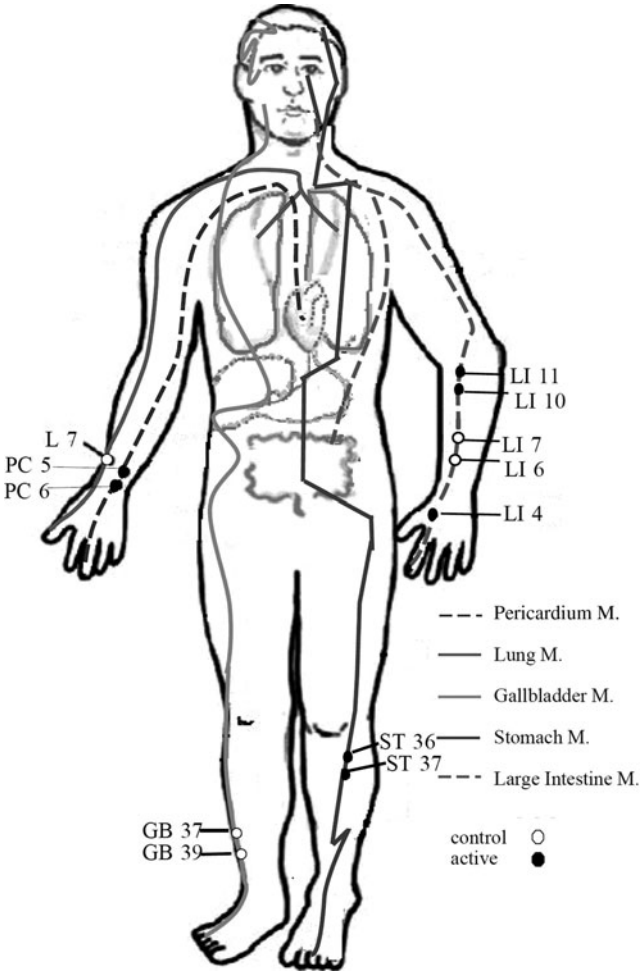

FIG. 1. Schematic of meridians and acupoints located on skin surface that have been demonstrated to exert strong cardiovascular action when stimulated (active points) as well as those that cause no cardiovascular response and that can be used as control points in studies of acupuncture regulation of the cardiovascular system. See text for additional discussion. Modified from Li and Longhurst[11] with permission of Elsevier. M., meridian.

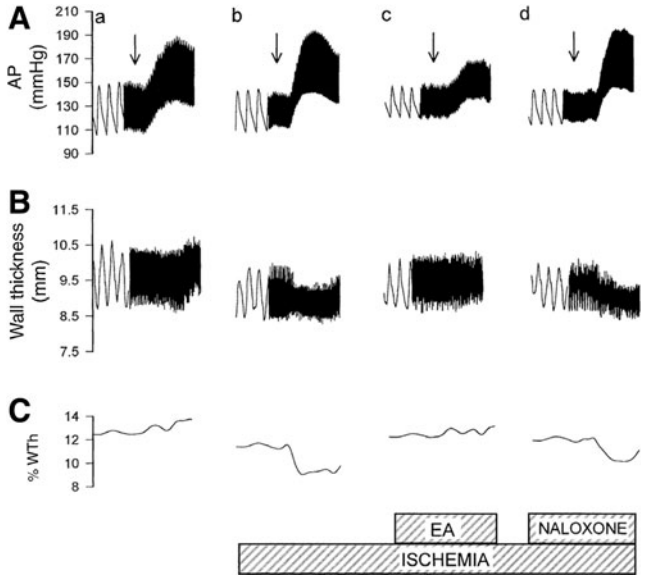

FIG. 2. Reflex increases in arterial blood pressure (AP; **Panel A**) and regional myocardial wall thickening measured with a sonomicrometer (**Panel B**). Beat-by-beat percent wall thickening (% WTh) also was calculated (**Panel C**). Bradykinin (BK) was applied to the gallbladder (arrows) to evoke visceral sympathetic reflex increases in AP and myocardial function **(Panel a)**. Following partial occlusion of a small branch of the left anterior descending coronary artery (LAD; **Panel b**) BK increased AP but reduced WTh, signifying regional ischemia (**Panel b**). Thirty minutes of electroacupuncture (EA) applied bilaterally at *Neiguan* and *Jianshi* acupoints (PC 5 and PC 6; see Fig. 1) on the forelegs diminished the reflex increase in AP and reversed the ischemic response (**Panel c**) while intravenous naloxone (**Panel d**) eliminated the action of EA on both AP and regional function. EA, therefore, is capable of reversing demand-induced myocardial ischemia through an opioid-sensitive mechanism. Modified from Chao et al.[12] with permission of the American Physiological Society.

reflexes initiated by gallbladder stimulation and gastric distension stimulate rVLM neurons by releasing the excitatory neurotransmitter glutamate to increase sympathetic outflow and raise BP.[23] Through these opioid mechanisms, acupuncture reduces glutamate release in the rVLM and hence modulates reflex sympathoactivation and elevated BP (Fig. 3).[23]

LONG-LOOP PATHWAY IN ACUPUNCTURE MODULATION OF EXCITATORY CARDIOVASCULAR REFLEXES

EA stimulation of somatic nerves applied for at least 10–15 minutes activates a ''long-loop'' pathway in the hypothalamus, midbrain, and medulla that leads to opioid-mediated regulation of rVLM neurons.[20] As part of this pathway, the arcuate nucleus in the ventral hypothalamus participates in modulation of BP elevations evoked by the defense reaction when EA is applied at the ST 36 and ST 37 acupoints located over the deep peroneal nerve.[4,24,25] Direct axonal projections from the arcuate to the rVLM are a source of β-endorphin for the rVLM.[20] Electrophysiological and anatomical studies recently have documented direct reciprocal projections between the arcuate and the midbrain ventrolateral periaqueductal gray (vlPAG), another important depressor region that processes somatic sensory input during EA (Fig. 4).[11,19,22,26,27] Both the arcuate and vlPAG receive input during EA at the PC 5, PC 6, ST 36, and ST 37 acupoints on the fore- and hindlimbs of cats, which are analogous anatomically to acupoints along the Pericardium and Stomach meridians on the wrists and lateral legs of humans.[20,28] The NRP in the midline medulla also forms part of the long-loop pathway activated during EA stimulation.[29] Indirect projections from the vlPAG to the rVLM though the

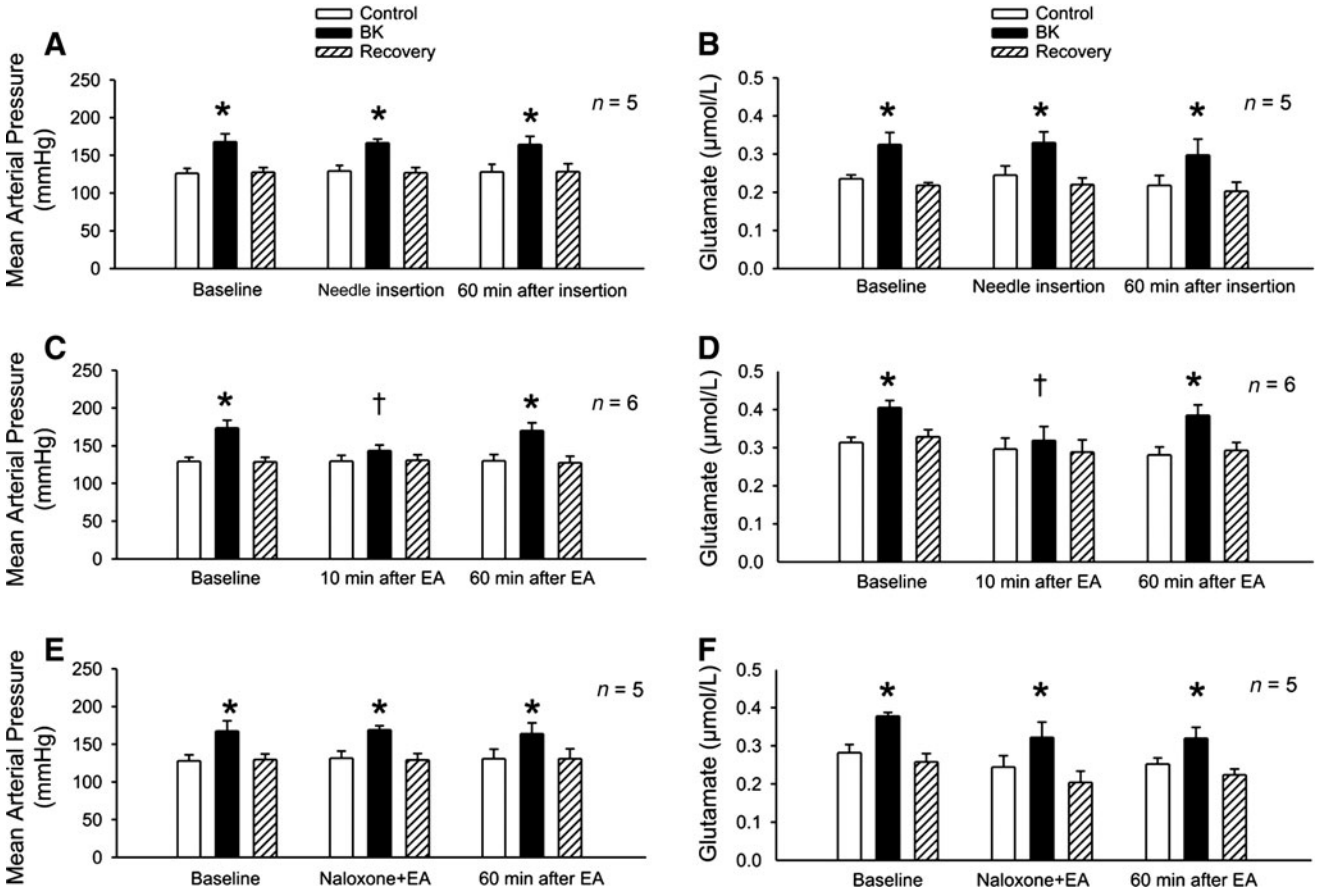

FIG. 3. Action of electroacupuncture (EA) on reflex blood pressure (BP) responses and rostral ventrolateral medullary (rVLM) extracellular glutamate concentrations (Glu) evoked reflexly by visceral afferent stimulation following application of bradykinin (BK) to the gallbladder before and after microperfusion of naloxone. Glu was assessed with high-performance liquid chromatography from sequential samples of dialysate recovered with microdialysis probes inserted into the rVLM. **Panels A and B** are controls showing that PC 5–PC 6 needle insertion without electrical stimulation does not alter BP or rVLM Glu responses to BK. **Panels C and D** show that EA significantly attenuated reflexes increases in BP and Glu evoked by visceral stimulation. **Panels E and F** show reversal of EA modulation of reflex-related increases in BP and Glu by naloxone. Thus, opioids in the rVLM during EA modulate the release of glutamate and sympathoactivation. Values are means ± standard error. $*p < 0.05$ versus control (before BK). $\dagger p < 0.05$ vs. baseline. Modified from Zhou et al.,[23] with permission of the American Physiological Society. min, minutes.

NRP are responsible for EA modification of reflex increases in BP.[30] Activation of the long-loop pathway through the arcuate, vlPAG, and NRP thus is critical for EA opioid–associated modulation of rVLM presympathetic neurons and differentiates EA's prolonged sympathoinhibitory action from the brief neural-occlusion response observed during short-term somatosensory stimulation.[14]

NEUROTRANSMITTER SYSTEMS UNDERLYING ACUPUNCTURE LONG-LOOP PATHWAY ACTIVATION

Stimulation by *glutamate* of both N-methyl-D-aspartate (NMDA) and non-NMDA or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionotropic receptors is responsible for EA-evoked activity in the arcuate and vlPAG.[27,30] The reciprocal excitatory pathway between the arcuate and the vlPAG reinforces and prolongs the action of EA on the reflex pressor responses. Both glutamate and *acetylcholine* are responsible for the excitatory connection from the vlPAG to the arcuate.[27] Conversely, glutamate but not acetylcholine underlies excitation in the vlPAG during arcuate stimulation. *Endocannabinoids* in the vlPAG reduce the release of *GABA* through presynaptic CB1 receptor stimulation during acupuncture, leading to disinhibition of neurons that project indirectly to the rVLM (Fig. 5).[31,32] *Serotonin* produced in EA-activated NRP neurons that project to the rVLM, through a 5-HT_{1A} mechanism, contributes to EA inhibition of rVLM sympathetic premotor neurons and acupuncture modulation of excitatory reflexes.[33] In addition, *GABA* and *nociceptin*, participate in EA-induced sympathoinhibition in the rVLM.[16,34]

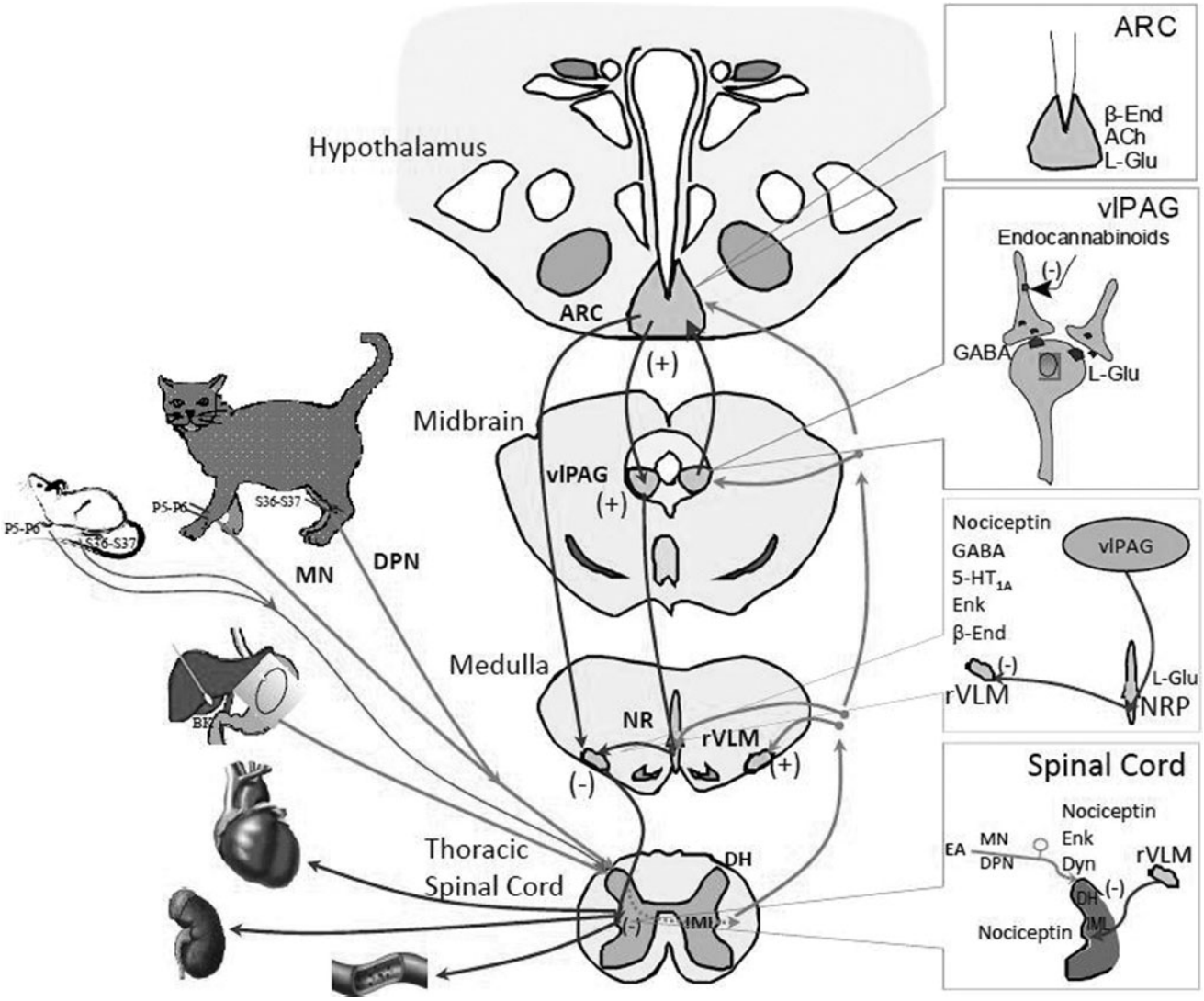

FIG. 4. Neural circuitry of acupuncture's action on visceral reflex–induced changes in cardiovascular sympathetic outflow following application of bradykinin (BK) to the gallbladder of cats or distension of the stomach in rats. Electroacupuncture at PC 5–PC 6 and ST 36–ST 37 somatic acupoints stimulates the median (MN) and deep peroneal nerves (DPN) evoking activity in the arcuate nucleus (ARC) in the ventral hypothalamus, ventrolateral periaqueductal gray (vlPAG) in the midbrain, nucleus raphé (NR)—especially the nucleus raphé pallidus (NRP)—and rostral ventrolateral regions of the medulla (rVLM) as well as the dorsal horn (DH) and intermediolateral column (IML) of the spinal cord. A number of neurotransmitters, including acetylcholine (ACh), L-glutamate (L-Glu), β-endorphin (β-End), endocannabinoids, γ-aminobutyric acid (GABA), met- and leu-enkephalin (Enk), serotonin or 5-hydroxytryptamine (5-HT), nociceptin, and dynorphin (Dyn) in the brain and spinal cord have been shown to participate in these brain nuclei by either activating (+) or inhibiting (–) neural activity evoked by the primary visceral reflex during EA modulation. The long pathway between the ARC and the rVLM illustrates the primary source of β-End. See text for details. Modified from Li and Longhurst[11] with permission of Elsevier.

SPINAL MECHANISMS IN ACUPUNCTURE–CARDIOVASCULAR MODULATION

Transcutaneous low-frequency pulsed electromagnetic stimulation, like acupuncture, inhibits reflex increases in BP through a naloxone-sensitive mechanism at the spinal level.[35] Enkephalins and dynorphin appear to predominate in spinal processing of the cardiovascular responses because the influence of magnetic stimulation is blocked by δ- and κ-, but not μ-opioid antagonists administered intrathecally.[35] Conventional EA likewise reduces visceral sympathoexcitation through both opioid and nonopioid (nociceptin) mechanisms in the spinal cord dorsal horn and intermediolateral column (IML).[36] EA's dorsal horn action implies inhibition of sensory inflow during reflex stimulation, while EA's action in the IML suggests that

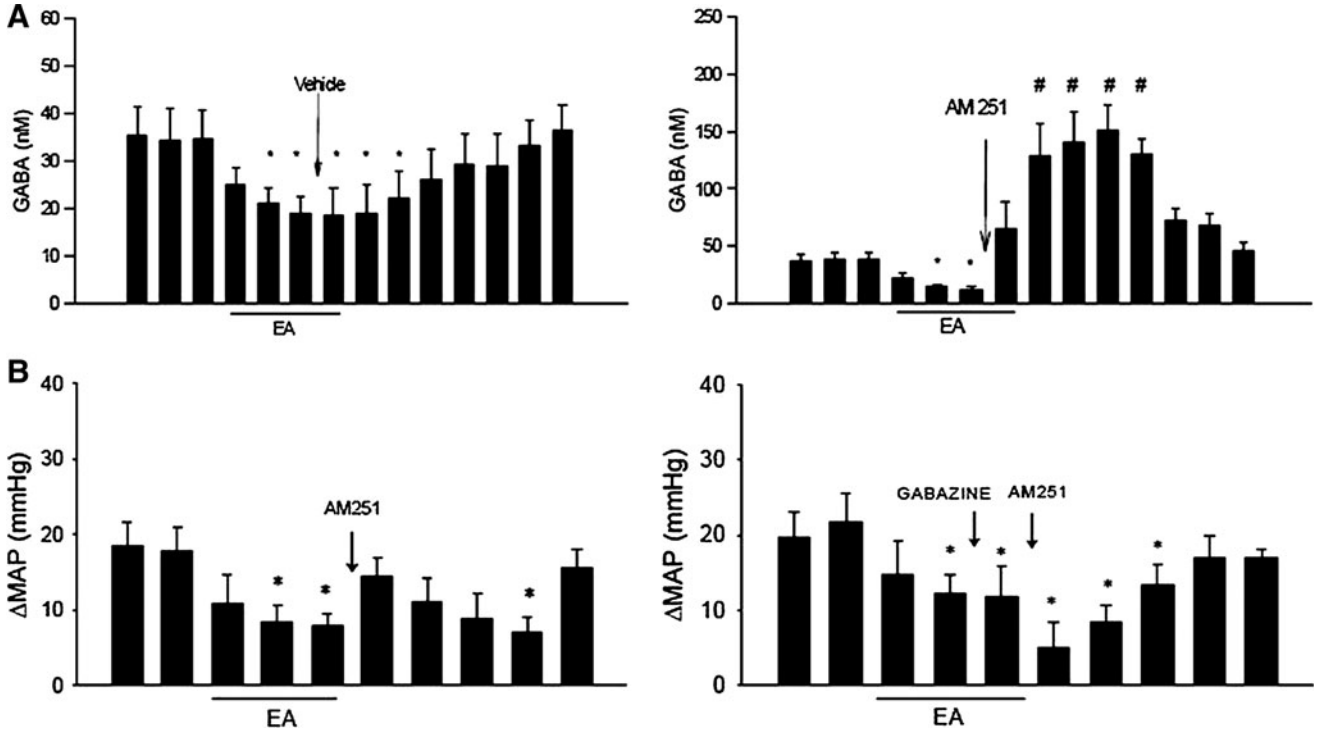

FIG. 5. Role of endocannabinoid system in electroacupuncture (EA) inhibition of visceral reflex–induced release of γ-aminobutyric acid (GABA) and changes in mean arterial blood pressure (ΔMAP). GABA concentrations were measured by high performance liquid chromatography from serial samples collected with a microdialysis probe inserted into the midbrain ventrolateral periaqueductal gray (vlPAG). EA suppressed the reflex increases in GABA and blood pressure (BP) by 40%–50% (**Panels A and B, left**). AM251, an endocannabinoid CB1 receptor antagonist, reversed the EA-associated decrease in GABA (**Panel A, right**) and BP (**Panel B, left**). Pretreatment with the $GABA_A$ antagonist gabazine eliminated the action of AM251 (**Panel B, right**), indicating that endocannabinoids act through GABA. Thus, EA in the vlPAG through a presynaptic CB1 receptor mechanism reduces the release of GABA to disinhibit neurons that participate in EA modulation of visceral reflex increases in BP. Values are means ± standard error. $*p < 0.05$ versus control (before EA); $p < 0.05$ versus EA inhibition. Modified from Fu and Longhurst[31] and Tjen-A-Looi et al.[32] with permission from the American Physiological Society.

acupuncture also modulates sympathetic outflow in the spinal cord.

MODULATION OF LOW BP BY ACUPUNCTURE

Several studies have explored the effect of acupuncture in various experimental models of hypotension. For example, acupuncture partially reverses hypotension associated with nitroprusside infusion or hemorrhage.[37,38] We have used two models to investigate the central regions and neurotransmitter systems involved in acupuncture's BP-raising capability. First, we used an I.V. infusion of the 5-HT_3 receptor agonist phenylbiguanide (PBG) to stimulate cardiopulmonary vagal afferent endings and reflexly evoke bradycardia and hypotension.[39–41] This model mimics vasovagal syncope, which is thought to be caused by mechanical stimulation of cardiopulmonary sensory nerve endings by a hypercontractile myocardium.[42,43] We found that preganglionic cholinergic (i.e., parasympathetic) neurons in the nucleus ambiguus in close proximity to axons containing enkephalin are activated by 30 minutes of EA.[44] In fact, during EA, both enkephalin and GABA in the nucleus ambiguus modulated PBG-evoked reflex vagal bradycardia (Fig. 6).[45] A second model of reflex hypotension involved gastric distension in hypercapnia-induced acidosis. Under these conditions, both spinal and vagal afferent pathways are stimulated by gastric distension to lower BP through a combination of sympathetic withdrawal and increased parasympathetic outflow.[46] Recent observations indicate that, through GABAergic mechanisms in the rVLM and caudal ventrolateral medulla (cVLM), EA limits the distension-related sympathetic withdrawal, while, in the nucleus ambiguus, EA inhibits the distension-induced increase in parasympathetic outflow and hence reduces the reflex hypotension and bradycardia.[47] No clinical studies on acupuncture's BP-raising actions are available, but it seems conceivable that acupuncture may be a therapeutic option for patients with recurrent vasovagal syncope or perhaps other forms of symptomatic hypotension.

Overall, consistent with Traditional Chinese Medicine (TCM) philosophy of achieving homeostasis, acupuncture

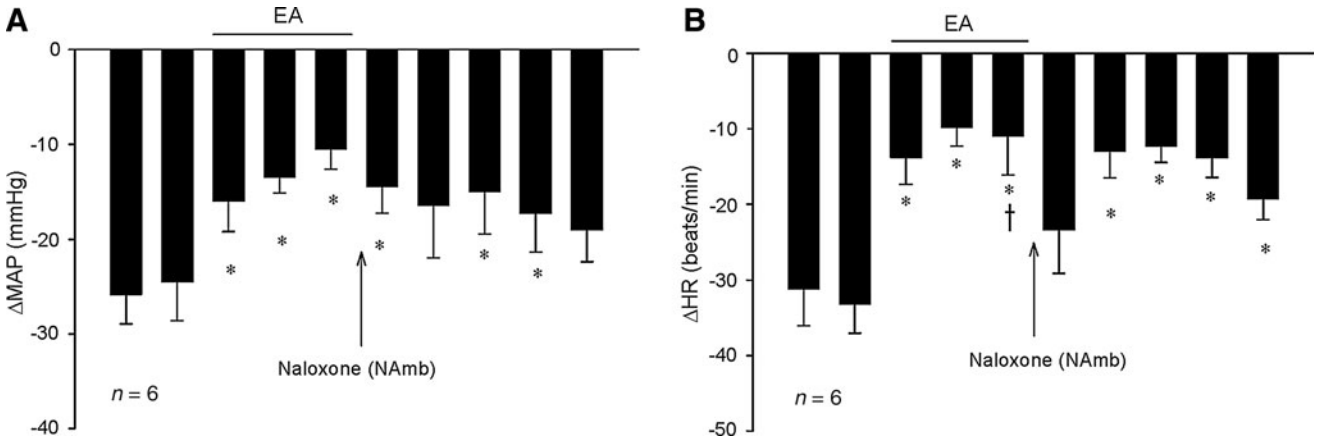

FIG. 6. Hemodynamic effects of electroacupuncture (EA) occurring through actions in the nucleus ambiguus (NAmb) of cats. Thirty minutes of EA reversed the reflex decreases in mean arterial blood pressure (ΔMAP) and heart rate (ΔHR) following intravenous (I.V.) phenylbiguanide (PBG) by 50%–60% (**Panel A**). Naloxone microinjected into the NAmb transiently reversed EA modulation of the bradycardia but not the depressor reflex (**Panel B**), indicating that opioids in the NAmb participate in EA modulation of parasympathetic outflow to the heart. Bars show means ± standard error. $*p < 0.05$ versus control (before EA). Modified from Tjen-A-Looi et al.[45] with permission of the American Physiological Society.

appears to be capable of normalizing BP by lowering elevated BP and elevating depressed BP. Somatic sensory nerve evoked input during acupuncture, acting through a number of neurotransmitter systems in several cardiovascular regions of the brainstem, essentially restores altered neuronal activity back toward a stable baseline. If, for example, the increase in activity is predominately sympathoexcitation, then acupuncture decreases the extent of excitation associated with increased sympathetic outflow and lowers elevated BP. However, if acupuncture is applied in the presence of reflex sympathetic withdrawal and/or increased parasympathetic outflow, the somatic sensory input activates modulatory neurotransmitter systems to reduce the extent of hypotension and bradycardia.

PERIPHERAL SENSORY NERVOUS SYSTEM IN ACUPUNCTURE

Acupuncture needles are typically inserted at acupuncture points (acupoints) located along meridians. Although many studies have attempted to locate meridians anatomically using a variety of anatomical and physiological methods, to date, the only reproducible and scientifically valid studies suggest that meridians are not physical entities but simply comprise a road map that guide acupuncturists regarding where to stimulate along the body's surface to evoke clinically meaningful responses.[25,48] Nerve bundles located beneath meridians are responsible for the action of acupuncture, and the only constant anatomical structures located in the vicinity of acupoints are nerves and nerve endings.[49] Thus, local anesthetic infusion into the region of an acupoint but not inflation of a BP cuff to suprasystolic pressures interrupts acupuncture analgesia.[50,51] Likewise, nerve transection abolishes acupuncture modulation of excitatory cardiovascular responses.[52] Interruption of sensory rather than motor nerve fibers is responsible for the influence of chemical or surgical denervation on the acupuncture–cardiovascular response, because motor paralysis does not influence acupuncture's action.[45] These studies prove that the nervous system, particularly somatic sensory nerve fiber stimulation underlies acupuncture's analgesic and cardiovascular actions. This conclusion is consistent with the clinical observation of many TCM practitioners who ask patients if they feel the sensation of De Qi, described by patients as a burning sensation, a fullness or heaviness in the extremity or trunk where acupuncture is applied. The therapist knows that an optimal clinical response will not be achieved without this neural sensation or paresthesia, thus confirming an important role for the sensory nervous system in acupuncture treatment.

Anatomical observations using light microscopy and multiunit recording studies suggest that myelinated sensory nerves conduct information centrally during acupuncture stimulation.[53–55] Neither procedure is capable of evaluating the role of small diameter Group IV afferents because they are not easily visualized or recorded. Group IV afferents are thought to convey nociceptive (painful) information to the CNS and, because acupuncture is not perceived to be painful, this sensory fiber type has not been thought to play an important role in signaling the brain during needling. However, single-unit afferent recording studies have demonstrated that acupuncture stimulates both finely myelinated Group III and unmyelinated Group IV afferent fibers in a ratio of 70:30.[9] Furthermore, when Group IV fibers are destroyed by capsaicin, acupuncture's hypotensive effect is nearly eliminated.[56] Thus, although low intensity EA stimulates many more Group III than Group IV sensory fibers and despite the fact that acupuncture typically is not a

painful stimulus, small-diameter, slowly conducting, unmyelinated, somatic sensory fibers constitute a necessary part of the afferent pathway for the cardiovascular actions of somatic acupuncture.

EXPLORATION OF UNIQUE FEATURES OF ACUPUNCTURE

Manual Acupuncture Versus EA

Our University's work has emphasized cardiovascular responses to EA because this form of acupuncture is easy to standardize. However, most acupuncturists use manual acupuncture, during which needles are inserted and then intermittently manipulated to strengthen the acupuncture response. To compare EA with the more commonly used manual acupuncture the magnitude and duration of acupuncture's hypotensive action was evaluated during and after 30 minutes of stimulation.[57] When the two modalities were matched for stimulation frequency (2 Hz) their impact on elevated BP was virtually identical, probably because the two forms of stimulation caused very similar activation of somatic sensory nerves, which link somatic needling with central neural modulation of sympathetic outflow.

Low-Frequency Versus High-Frequency EA

Studies of acupuncture analgesia suggest that both low- and high-frequency EA (2 and 100 Hz, respectively) raise the pain threshold, although to some extent in different locations in the brain and through different neurotransmitter mechanisms. Low-frequency EA used to treat pain appears to be linked to the action of enkephalins, while high-frequency EA is associated with dynorphin acting in different regions of the brain.[3,58] However, a study of EA's action on cardiovascular function led to a different conclusion.[57] Thus, while low-frequency (2 Hz) EA at PC 5 and PC 6 reduced sympathoexcitatory BP responses by $\sim$40%, neither middle- (20–40 Hz) nor high-frequency (100 Hz) EA influenced these reflex responses. Low-frequency EA led to much greater activation of afferent fibers than higher frequencies of stimulation, indicating that, with the latter form of stimulation, there is simply less information traveling centrally to inhibit presympathetic activity in regions such as the rVLM. Differences between studies from China showing that high-frequency EA modulates pain effectively and our studies demonstrating that there is no discernible influence of high-frequency acupuncture on elevated BP presently cannot be reconciled. Further research is warranted.

Acupoint Combinations

The first treatise on acupuncture, the *Inner Classic of the Yellow Emperor*, published between 100 and 200 BC described 160 acupoints.[59] This number has been gradually expanded first to 349 in the *A–Z Classic of Acupuncture and Moxibustion* published in 300 AD, and, more recently, to 361 acupoints in modern textbooks.[60,61] Clinical acupuncture typically involves stimulation of several acupoints in combination, presumably to reinforce and increase acupuncture's action.[57,62] Early studies on acupuncture's role in pain suggested that using a combination of two points, for example *Hoku* or *Hegu* (LI 4) located along the Large Intestine meridian between the thumb and the first finger (over branches of the radial and median nerves) and *Zusanli* (ST 36) along the Stomach meridian on the lateral leg just below the knee over the deep peroneal nerve, produced a greater effect using either one acupoint alone.[63] However, using EA to control the magnitude and frequency of stimulation precisely—and hence input to the CNS—we found that bilateral stimulation of two combinations of acupoints (PC 5–PC 6 and ST 36–ST 37)—which evoke strong cardiovascular responses independently—does not evoke larger decreases in elevated BP than stimulation of each individual set of acupoints.[15,57] More studies on the potential additive or synergistic effects of stimulating combinations of acupoints—including, for example, combinations of somatic and auricular acupoints—to maximize clinical responses are needed.

Point Specificity

An important concept in TCM is point specificity, which implies that stimulation of some acupoints are important for addressing certain clinical conditions, whereas other acupoints are less effective or are ineffective. A systematic review of 12 studies was designed to answer the question: ''Are acupoints specific for diseases?'' The reviewers concluded that approximately half of the trials produced evidence for point specificity and half did not.[64] However, a number of trials included in this review were biased. Five with a low risk of bias showed no difference between sham and true acupuncture. Thus, support for the concept of point specificity has been weak and several questions have emerged. First, if point specificity does not exist, can appropriate controls that incorporate acupoints, which are inactive in certain conditions, be developed for acupuncture? Use of such controls to assess sham actions of acupuncture allows rigorous investigation of its point-specific clinical actions, an underlying tenet of acupuncture philosophy. However, there are many studies in the acupuncture literature that either do not incorporate control stimulation or that use weak controls.[65] Second, are rigorous studies available that show clear point-specific responses and, if such studies have been conducted, what was the underlying mechanism of point specificity? Dr. Han argues from a neurobiological perspective that there is an uneven distribution of nerves along the body, so it is irrational to assume that needling different places would elicit the same response.[3] Furthermore,

it is unlikely that all sensory neurons project identically to centers in the brain and, as such, stimulation of different acupoints along separate neural pathways should evoke quite different acupuncture responses. In a study examining potential answers these questions from a cardiovascular perspective, we showed that point-specific responses to EA at different acupoints exist.[15] Stimulation of some points results in significant reductions in elevated BP, while others cause more-modest changes or no change at all. In general, stimulation of acupoints (PC 5, PC 6, ST 36, ST 37, LI 4, LI 10, and LI 11; Fig. 1) located over deep somatic nerves, such as the median or deep peroneal nerves, reduced elevated BP, whereas EA at acupoints (LI 6, LI 7, KI 1, BL 67; Fig. 1) located over superficial (cutaneous) nerves, such as the superficial radial and tibial nerves, have produced little cardiovascular effect.[11] Stimulation of nerves underlying acupoints that reduced elevated BP the most during EA evoked the greatest rVLM discharge activity (Fig. 7) suggesting that ''hard wiring'' of somatic nerves that project indirectly to regions of the brain concerned with regulation of sympathetic outflow underlies the capability of certain acupoints to lower BP effectively.[15] As noted above in the first question posed, our study also has implications for selection of effective controls for future studies of acupuncture in both experimental and clinical situations. We have found that it is possible to use either (1) inactive acupoints or (2) active acupoints in which a needle is placed but not stimulated as two strong controls, which can be compared with responses to stimulation of active acupoints.[57] In the former paradigm, there is little input to cardiovascular centers of the brain, while, in the latter, there is brief, transient but not sustained sensory stimulation and hence a negligible influence of sham acupuncture over and above placebo. Yet, in both cases, acupuncture needles are inserted and underlying neural pathways are stimulated (at least briefly) to evoke De Qi, which cannot be differentiated by patients. Certainly, the debate over the existence of point specificity is likely to continue. It is difficult to resolve this question in humans in whom placebo may play a role during acupuncture, because stimulation of any point is perceived consciously and may be believed by patients to potentially offer relief. However, it does seem clear, from experimental and even clinical studies, such as in our laboratory, that point-specific responses can occur when the acupuncture stimulus and experimental paradigm are controlled carefully.[66]

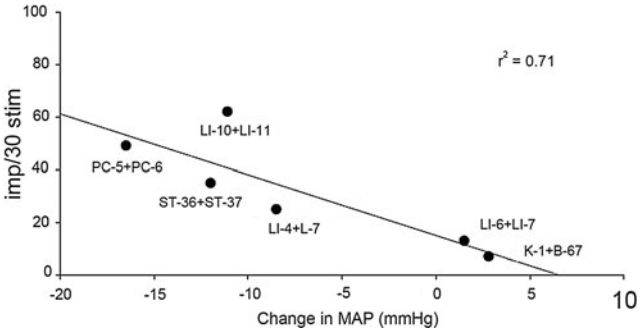

FIG. 7. Relationship between changes in mean arterial blood pressure (MAP) and evoked activity displayed as impulses (imp) in the rostral ventrolateral medulla (rVLM) during electroacupuncture (EA) modulation of visceral sympathoexcitation. EAwas maintained at low frequency (2 Hz) for 30 minutes, while evoked activity in the rVLM consisted of needle stimulation at the same acupoints and frequency for 15 seconds. A strong correlation was observed between acupoints that evoked large increases in rVLM activity and decreases in the reflex increases in MAP (e.g., PC 5–PC 6) as well as those that evoked little activity in this medullary region and did not influence the reflex sympathoexcitation, indicating that acupoints overlying nerves that project to a region of the brain that is known to regulate sympathetic activity are most capable of influencing cardiovascular function through their actions on autonomic outflow. See Fig. 1 and text for explanation of acupoint nomenclature. Stim, stimulation. Modified from Tjen-A-Looi et al.[15] with permission of the American Physiological Society.

DISCUSSION

Despite tremendous advances in understanding of how acupuncture works, a number of unanswered or partially answered questions remain in acupuncture research.

Are Experimental Studies Applicable to Clinical Acupuncture?

The answer is probably ''yes.'' As shown by our experimental findings, application of EA does not alter BP when it is not elevated but does reduce exercise-associated pressor responses in human subjects.[67] Currently, preliminary ongoing studies of acupuncture in patients with mild-to-moderate hypertension suggest that using acupoints demonstrated experimentally to have the greatest influence on reflex elevations in BP—and using a stimulus paradigm that is most effective (low-frequency, low-intensity EA bilaterally at PC 5, PC 6, ST 36 and ST 37 applied once weekly for 30 minutes)—reduces systolic and, to a lesser extent, diastolic arterial BP by 8–12 mmHg in $\sim$70% of patients studied.[66] The reduction in BP is slow in onset, beginning 2–4 weeks after initiating EA, and is prolonged in duration, extending for several weeks after termination of an 8-week trial of acupuncture. More patients need to be evaluated and compared to control acupuncture involving treatment at inactive cardiovascular acupoints, to verify that the observed responses are not a placebo effect. In addition, ongoing experimental studies of nonanesthetized hypertensive conditions (conscious rats in a cold environment) subjected to repeated acupuncture may provide additional clues about how to best apply acupuncture clinically.

Why Does Acupuncture Have a Prolonged Action?

Experimental studies involving anesthetized preparations demonstrate that cardiovascular hypotensive responses to acupuncture typically last for 1–1.5 hours beyond the period of stimulation.[16] As discussed above, this prolonged action in response to 30 minutes of stimulation, in part, is related to activation of a long-loop hypothalamic–midbrain–medullary pathway, which leads to the release of a number of inhibitory neurotransmitters that ultimately modify sympathetic outflow.[25] Within the long-loop pathway reciprocal excitatory projections between the arcuate nucleus in the hypothalamus and the vlPAG in the midbrain reinforce and prolong the acupuncture-evoked somatic input and hence EA's action on elevated BP.[19,22,26,27] Also, both opioids and GABA in the rVLM participate in the prolonged response to a single application of acupuncture in anesthetized animals.[16] However, additional mechanisms underlying EA's prolonged action appear to be operative when acupuncture is applied repeatedly over a period of days, weeks, or months. In this regard, a single application of acupuncture over 30 minutes stimulates preproenkephalin mRNA expression, the precursor of enkephalin, for a period lasting 90 minutes.[68] Repeated acupuncture over several days causes longer elevations of the message and protein (enkephalin) expression, lasting hours or days after acupuncture is terminated.[44] So, through transcriptional and possibly translational regulation of the precursors of modulatory neurotransmitters, such as enkephalins, repeated acupuncture exerts a very prolonged action on BP. More experimental and clinical studies are needed to determine how often acupuncture treatment must be reinforced to continue to suppress elevated BP after an initial period of application that lowers it effectively.[66] Our current hypothesis is that continued treatment can maintain low BP effectively, when it treatment is given once or twice each month.

How Can Acupuncture Effectiveness Be Improved?

Studies from a number of groups studying acupuncture analgesia indicate that $\sim$70% of patients respond to acupuncture.[62,69–72] We have made similar observations in studies evaluating cardiovascular responses to acupuncture.[66,67] But why are some individuals unresponsive to acupuncture treatment? Recent preliminary investigations in the University's laboratory suggest that nonresponders can be converted to responders by administering an antagonist to the octapeptide of cholecystokinin.[73] Cholecystokinin (CCK) is produced in the intestine, where CCK delays gastric emptying, contracts the gallbladder, releases bile and causes secretion of pancreatic enzymes. The octapeptide of CCK or CCK-8 is distributed widely throughout the brain.[74,75–77] CCK in the brain antagonizes the action of morphine, leading to tolerance, a form of nonresponsiveness.[78–80] CCK-8 exerts an antiopioid effect in the brain.[78,81] Molecular studies suggest that CCK, through a CCK-A receptor mechanism in the hypothalamus, may reduce responsiveness to EA.[82–84] Recent preliminary studies suggest that CCK-8 in the rVLM, through a CCK-A receptor mechanism, contributes to the absence of EA's antihypertensive action in rats.[73] These studies may provide clues for conversion of some EA nonresponders into responders.

CONCLUSIONS

Laboratories in China and the United States have begun to elucidate the mechanisms through which acupuncture reduces pain and cardiovascular dysfunction, including myocardial ischemia, hypertension, and hypotension. Over the last two decades, substantial information has been developed to show that acupuncture acts mainly through the peripheral nervous system and the CNS. It is now known that acupuncture leads to the release of a number of excitatory and inhibitory neurotransmitters in the CNS to alter processing of sensory information and, ultimately, autonomic outflow, and hence cardiovascular function. It has been exciting to play a role in developing new knowledge of the mechanisms of acupuncture's cardiovascular actions. However, while the information base has been considerably expanded, much work remains to be accomplished to understand fully the clinical actions of this ancient therapy.

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