Implication of Neuromodulation Therapy by Electroacupuncture in Treatment of Diabetes

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Abstract
Diabetes affects approximately 366 million individuals worldwide. Current pharmacological therapy is not perfect, and often is associated with adverse side effects. Acupuncture is used as an adjunctive treatment for a number of cardiovascular diseases. Chronic activation of the sympathetic nervous system has emerged as a key player in both the pathogenesis and progression of diabetes and metabolic syndrome. Recent evidence indicates that the down regulation of central nitric oxide system leads to an increased renal sympathetic neural activity in diabetic rats. Our experimental studies have shown that electroacupuncture stimulation exerts sympathoinhibitory effects through activation of neurons in the rostral ventrolateral medulla. This brief review will discuss current knowledge of the effects of acupuncture on central nervous system and provide a perspective on the future of treatment of diabetes with this alternative medicine technique.

Keywords: Central nervous system; Electroacupuncture; Neurotransmitter; Brain stem

Introduction
Cardiovascular diseases are the most common cause of mortality worldwide. Diabetes and hypertension are the major risk factors in the development of cardiac hypertrophy, ischemic heart disease and cardiac failure. The prevalence of diabetes increases with age, the lifetime risk of developing diabetes approaches approximately 32.8% for males and 38.5% for females [1]. Although treatment strategies [2-4] targeting blood pressure, blood glucose, triglycerides, and low-density lipoprotein cholesterol levels, along with lifestyle modifications have been developed for this disease, treatment has not yet been perfected and often is associated with adverse side effects.

Acupuncture is increasingly being accepted as an alternative medical therapy in the United States. Manual acupuncture and its potent alternative, electroacupuncture (EA), have been used in Asia to treat a number of cardiovascular diseases including myocardial ischemia, hypertension, and diabetes [5-7]. Many western physicians, however, are reluctant to recommend acupuncture because its actions in the treatment of diabetes remain controversial and because the physiological mechanisms determining its response are largely unknown to practitioners of western medicine. This brief review will discuss current knowledge of the effects of acupuncture on central nervous system and provide a perspective on the future of treatment of diabetes with neuromodulation therapy such as EA.

Effects of Acupuncture on Diabetes in Experimental and Clinical Studies
Acupuncture is a 3000-year-old form of traditional Chinese medicine that involves inserting needles at specific points along specific meridians on the body to help treat diseases or pain that result from imbalances of energy flow – ‘Qi’. The old acupuncture needles were made of bronze, silver and gold. Today, most acupuncturists use disposable stainless steel needles ranging in length (0.5–100 mm) and gauge (0.12–0.30 mm). The depth of insertion varies from shallow (1–2 mm) to deeper needling (50–60 mm). Variable methodology can lead to different responses. For example, we have found that electroacupuncture (EA) at the acupoints overlying the deep somatic nerves exerts inhibitory effects on cardiovascular reflex responses, while EA at those overlying the superficial nerves does not, suggesting that point specificity exists in acupuncture treatment [8].

Recently, Peplow and Baxter performed a literature review on electroacupuncture for control of blood glucose in diabetes [5]. Only two studies were found using EA in human subjects, and they indicated that electroacupuncture treatment lowered the blood glucose level in obese patients and healthy subjects [9,10].

EA at 15 Hz for 30 minutes at Zusani and Zhongwan’s acupoints lowered the blood glucose level in fasted type I [11,12] and II diabetic rats [13-15] as well as in fasting, normal rats [16]. Additionally, at these same acupoints in hyperglycemic rats, EA resulted in decreased glucose levels with elevated serotonin and endogenous opioids [11,17].

Interactions between the Autonomic Nervous System and Diabetes
The autonomic nervous system (ANS) - subdivided into the parasympathetic and sympathetic branches - is crucial in regulating glucose metabolism, thus mediating insulin secretion and absorption. Studies have indicated that ANS impairment shares an interchangeably causal relationship with diabetes.

One potential cause for elevated sympathetic activity is the genetic polymorphism of beta-2 and -3 adrenoreceptor genes which have

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been directly associated with diabetes [18]. Sympathetic overactivity may also be caused by the activation of the renin-angiotensin system, contributing to hypertension in diabetic patients with chronic renal failure [19]. Hyperinsulemia – a promoter of diabetes - can also trigger the sympathetic system, increasing peripheral resistance and sodium retention, increasing the risk for hypertension [19]. Moreover, cardiac autonomic remodeling has also been demonstrated in diabetic rats [20]. Effective refractory period (ERP) typically shortens during sympathetic stimulation, but unlike their healthy counterparts, the diabetic rats displayed increased heterogenous atrial ERP and altered sympathetic nerve histology (seen through tyrosine hydroxylase staining), thus making them more susceptible to atrial fibrillation [20].

In retrospect, sympathetic overactivity causes the diabetic heart to metabolize fatty acids instead of glucose, resulting in insulin resistance, accumulation of lipid metabolites, increase in oxidative stress and myocardial fibrosis [21]. These conditions decrease contractile capacity in addition to abnormal diastolic and systolic function. To compensate for this decrease in systolic function, the sympathetic nervous system (SNS) is activated, initiating the diabetic heart to increase sympathetic tone [21]. Furthermore, as epinephrine and norepinephrine are known markers for sympathetic stimulation, elevated levels were found in type I diabetic patients at high risk for chronic renal failure and the progression of nephropathy [19]. In patients with type II diabetes, sympathetic overactivity often contributes to insulin resistance, stimulating skeletal muscle alpha- and beta-adrenergic receptors, thus decreasing vasodilation and contributing to the development of hypertension [22-25].

Hyperglycemia – directly linked with caloric intake and body mass index – may explain further why the prevalence of hypertension is higher in type II versus type I diabetic patients [26].

Considering the other opposing branch of the ANS, the parasympathetic system stimulates pancreatic beta cells to secrete insulin, whereas the sympathetic branch blocks the secretion of insulin [23]. Vagal impairment can lead to sympathetic overactivity, consequently promoting the reabsorption of sodium, increasing stroke volume, heart rate and vascular resistance [19]. These all serve as risk factors for cardiovascular disease and hypertension, viable players in the formation of diabetes. Studies have also indicated that young adults with impaired vagal reactivation tend to be more hyperinsulinenic [23]. Additionally, chronic hyperglycemia promotes progressive autonomic neural dysfunction in a manner paralleling the development of peripheral neuropathy [27]. Interestingly enough, neuropathy is first seen in the longest, autonomic neural fiber, the vagus nerve. This is often seen in patients with cardiac autonomic neuropathy (CAN) [27]. The initial parasympathetic denervation and increased sympathetic tone leads to nocturnal hypertension in diabetics, shortly followed by sympathetic denervation or orthostatic hypotension. One of the earliest symptoms of CAN is heart rate variability, but further progression of this disease can lead to arrhythmias and sudden cardiac death [28].

Autonomic nervous system dysfunction underlies obesity by decreasing insulin sensitivity and endothelial function while increasing oxidative stress, myocardial fibrosis and causing hyperinsulemia and hypertension; these are all mechanisms associated with the development of diabetes [29]. However, the diabetic condition and sympathetic overactivity are in close interaction, and possessing one of the conditions exacerbates the other. It is clear that the sympathetic nervous system plays a key role in both the pathogenesis and progression of diabetes and metabolic syndrome (Figure 1).

Over the past decade, we have examined the central neural regulation of sympathoexcitatory reflex by acupuncture in different regions of brain, including the rostral ventral lateral medulla (rVLM), hypothalamic arcuate nucleus (ARC), midbrain ventrolateral periaqueductal gray (vPAG) nuclei, medullary nucleus raphe pallidus (NRP) and dorsal horn and intermediolateral column of the spinal cord.

**EA Inhibition of Neural Activity in the rVLM**

The rVLM plays a critical role in the regulation of sympathetic outflow and blood pressure (BP) [30]. Inhibition of neuronal function in this nucleus results in significant BP decreases [31]. We have demonstrated previously that both low frequency electro- and manual acupuncture inhibit the pressor response as well as premotor sympathetic neural firing in the rVLM [32]. Administration of naloxone (non-specific, opioid receptor antagonist) or gabazine (γ-aminobutyric acid or GABA type A receptor blocker) in the rVLM abolishes EA modulation [33]. The rVLM is an important brain stem region that processes somatic inputs during acupuncture stimulation. When compared to cardiovascular inactive acupoints (LI 6-7, G 37-39) over superficial afferent nerves, electrophysiological studies of neuronal activity in the rVLM have shown that P 5-6 as well as LI 4-11 over the deep median and radial nerves provide more afferent input to cardiovascular premotor sympathetic neurons in the rVLM [8]. This observation likely explains why acupuncture over these deep nerves most effectively lower elevated sympathetic outflow and BP.

**Neurotransmitters in rVLM, ARC and vPAG**

Early studies suggested that EA attenuates the sympathoexcitatory reflex responses through the release of opioids, GABA, nociceptin and serotonin (or 5-hydroxytryptamine, 5-HTT) in the rVLM [34-38]. We have demonstrated that the EA inhibition of sympathoexcitatory reflex response in cats is related to the activation of μ- and δ-, but not κ-opioid receptors in the rVLM, suggesting that endorphins, enkephalins and perhaps endomorphin, but not dynorphin are mainly responsible for EA modulation of cardiovascular responses.

Immunochemical staining studies have demonstrated the...
presence of enkephalergic neurons in the rVLM and endorphinergic neurons in the ARC that project directly to the rVLM, and that both neurotransmitter systems are activated by EA [39]. EA inhibits the sympathetic reflex response through opioid-mediated inhibition of glutamate in the rVLM [40]. Electrophysiological studies [41] have determined that reciprocal excitatory glutamatergic (NMDA and non-NMDA) projections exist between the ARC and vIPAG that may participate in the EA inhibition of sympathetic nerve activity. This reciprocal projection may include a cholinergic component in the ARC but not in the vIPAG [42].

Furthermore, EA, through presynaptic endocannabinoid CB1 receptor stimulation, reduces the vIPAG release of GABA but not glutamate during EA [43]. Reduced GABA disinhibits vIPAG neurons, thus increasing their activity, which, in turn, through an action in the NRP inhibits rVLM cardiovascular sympathetic neurons and related sympathoexcitatory reflex responses [44]. Therefore, it is clear that a variety of neurotransmitter systems underlie the cardiovascular modulation of EA. This includes both excitatory and inhibitory neurotransmitters, with their importance varying between the different nuclei.

Long-Loop Pathway for EA Cardiovascular Modulation

The role of the hypothalamic ARC and its interaction with the vIPAG and rVLM in the EA-cardiovascular sympathoexcitatory responses has been extensively studied [8,37,45,46]. Microinjection of the excitatory amino acid DL-homocysteic acid (DLH) into the ARC augments the responses of vIPAG neurons, while microinjection of small volumes (50 nl) of kainic acid (KA) causes a reversible depolarization blockade that transiently deactivates arcuate neurons and decreases the vIPAG responses to splanchic nerve (SN) stimulation [37]. Additionally, EA increases SN-evoked discharge of vIPAG neurons, a response that can be blocked by microinjection of KA into the ARC. Microinjection of DLH into the ARC, like EA, inhibits the sympathoexcitatory reflex induced by application of bradykinin to gallbladder for approximately 30 min. Finally, microinjection of KA into the ARC blocks the inhibitory influence of EA on the sympathetic pressor reflex. As such, these results suggest that excitatory projections from the ARC to the vIPAG appear to be essential to the inhibitory influence of EA on the pressor reflex induced by SN and gallbladder afferent stimulation.

**vIPAG-rVLM Projections**

The vIPAG provides inhibitory input to premotor sympathetic neurons in the rVLM to ultimately reduce sympathetic outflow and reflex elevations in BP [46]. Direct axonal projections from the vIPAG to the medulla have been documented in tract tracing studies [47]. However, a vIPAG projection to the raphé, in particular the nucleus raphé obscurus (NRO), also exists and has been thought to form an indirect pathway from the vIPAG to the rVLM that is involved in the EA-cardiovascular response [48]. However, recent studies have suggested that the NRP, located more ventrally than the NRO or the nucleus raphé magnus, contains more cells activated during median nerve stimulation with EA at the P 5-6 acupoints, as judged by the concentration of c-Fos labeling [49]. Chemical blockade of the NRP with KA or kynurenic acid transiently reverses activation of neurons in the rVLM during stimulation of the vIPAG as well as EA modulation of visceral excitatory reflexes [50]. Furthermore, the NRP inhibits rVLM activity, including activity of bulbospinal premotor sympathetic neurons. Serotonin projections from the raphé acting on 5-HT1A receptors in the rVLM complete the vIPAG-NRP-rVLM circuit to modulate cardiovascular activity [50]. Thus, an indirect connection from the vIPAG to the rVLM involving a serotonergic connection between the NRP and the rVLM plays an important role in the long-loop modulation of cardiovascular sympathetic outflow during reflex visceral stimulation. These studies do not eliminate the possibility that direct projections between the vIPAG and the rVLM also might serve a functional role in EA-cardiovascular modulation. The direct or indirect projections from the vIPAG to the rVLM complete the long-loop pathway and provide an important source for the inhibitory influence of EA on rVLM premotor neurons and ultimately sympathoexcitatory cardiovascular responses [48].

**ARC-rVLM Projections**

As noted previously, neurons in the vIPAG receive convergent input from a number of somatic nerves stimulated during EA, as well as from the ARC. Bilateral microinjection of KA into the rostral vIPAG partially reverses rVLM neuronal responses and cardiovascular inhibition during DLH stimulation of the ARC. Conversely, depolarization blockade of the caudal vIPAG completely reverses arcuate-evoked rVLM responses [48]. In parallel studies, we have observed that arcuate neurons can be antidromically activated from the rVLM and that arcuate perikarya are labeled with a retrograde tracer microinjected into the rVLM [48]. Many neurons from the arcuate that project to the rVLM are activated by EA stimulation (c-Fos-positive) and they frequently contain opioid peptides, particularly β-endorphin [51]. As such, the vIPAG, particularly the caudal vIPAG, appears to be required for inhibition of rVLM neuronal activation by the ARC and subsequent EA-related cardiovascular activation. However, direct projections from the ARC to the rVLM, likely serve as an important source of β-endorphin since this projection contains this opioid peptide [48]. This latter observation is consistent with our earlier anatomical study showing that cells in the rVLM contain enkephalin but not β-endorphin [51]. Hence, EA-cardiovascular responses that result from the action of β-endorphin on µ-opioid receptors located on rVLM sympathoexcitatory premotor neurons depend on this hypothalamic-medullary projection [52].

**Role of Spinal Cord in Acupuncture-Cardiovascular Response**

The spinal cord processes somatic and visceral reflexes as well as outputs from the central nervous system to effector organs involved in cardiovascular reflex regulation [53]. Anatomical and physiological studies indicate that the dorsal horn of the spinal cord serves as a major center for EA-induced analgesia [54,55]. Both low- and high-frequency EA at Zusani (St 36) acupoint increase Fos immunoreactive neurons in the superficial laminae (I and II) in the dorsal horn of the spinal cord [55]. Since opioid or nociceptin-like immunoreactivity is present in the spinal sympathetic nuclei (i.e. intermediodorsal column, IML) [56,57], we have considered the possibility that EA also influences the neurotransmission between the brain stem and the IML [58]. In this regard, our studies have found that both opioid and nociceptin reduce the response to rVLM-induced sympathoexcitatory modulation, indicating that the two peptides can regulate sympathetic outflow [59,60]. In addition, there has been a suggestion that descending pathways from the brain stem (presumably to the dorsal horn of the spinal cord) may influence the segmental processing of somatic inputs during EA [61,62]. Afferent stimulation can modulate sympathetic activity through the inhibition of excitatory interneurons [63]. Furthermore, somatic stimulation can elicit excitatory and inhibitory responses in both IML and dorsal horn interneurons, depending on the dermatome stimulated [64]. These interneurons appear to form important links in the spinal cord circuitry involved in autonomic control [65]. Taken together, these
results indicate that opioid and nociceptin play a role in the processing of spinal cord interneuron activity in the EA response. However, spinal circuits controlling the cardiovascular visceral reflex responses during EA require further elucidation.

Summary

EA inhibits the sympathetic outflow by modulating the activity of cardiovascular presympathetic neurons in the rVLM. Activation of neurons in the ARC of the hypothalamus, vIPAG in the midbrain and NRP in the medulla by EA can inhibit the activity of premotor sympathetic neurons in the rVLM. Glutamate, acetylcholine, opioids, GABA, nociceptin, serotonin, NO, endocannabinoids in the brain all appear to participate in the EA sympathoinhibitory response (Figure 2). Since the ANS plays an important role in the glucose metabolism, modulation of sympathetic outflow are presumed to be the mechanisms underlying the hypoglycemic effects of acupuncture. Previous studies have demonstrated that EA reduces the plasma glucose levels by increasing insulin production and improves insulin sensitivity by inducing secretion of endogenous β-endorphin [66] and serotonin [67]. Lee et al. recently have shown that EA at ST36 acupoints induce a hypoglycemic effect by stimulating the cholinergic nerve in diabetic rats [68,69]. Taken together, these results provide a strong link between the central acupuncture and the treatment of diabetes.

Future Perspective

The conventional medical treatments for diabetes are not perfect and can lead to serious side effects [70,71]. Increasing evidence has demonstrated that Traditional Chinese Medicine including acupuncture can treat diabetes [13,72,73]. EA has been shown to lower blood glucose and increase insulin sensitivity with no side effects [13,15,67]. We would suggest that lifestyle changes and other integrative approaches such as acupuncture could serve as initial treatment for diabetes before drug therapy. In diabetic patients who already receive drug therapy, lifestyle modifications and alternative therapies, particularly acupuncture, can further reduce blood glucose and potentially allow patients to reduce dosages of standard hypoglycemic agents. However, further research comparing acupuncture with drug regimens in diabetes is required.

References


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