Journal of Diabetes and Metabolism
ISSN: 2155-6156

Zhou et al., J Diabetes Metab 2013, 4:5
DOI: 10.4172/2155-6156.1000270

Review Article Open Access

Implication of Neuromodulation Therapy by Electroacupuncture in Treatment of Diabetes

Wei Zhou[1]*, Eileen L So[2], Kentaro Yamakawa[1] and Aman Mahajan[1]

[1]*Department of Anesthesiology, University of California, Los Angeles, USA*
[2]*Cardiac Arrhythmia Center; University of California, Los Angeles, USA*

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 arcuate nucleus, ventrolateral gray, and nucleus raphe to inhibit the neural activity 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 Zusanli 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

***Corresponding author:** Wei Zhou, David Geffen School of Medicine, University of California, 650 Charles E Young Dr S, CHS 56-131, Los Angeles, CA 90095, USA, Tel: 310-825-2204; Fax: 310-825-8608; E-mail: wzhou@mednet.ucla.edu, isamusyuu@gmail.com

Received May 24, 2013; **Accepted** June 24, 2013; **Published** June 30, 2013

Citation: Zhou W, So EL, Yamakawa K, Mahajan A (2013) Implication of Neuromodulation Therapy by Electroacupuncture in Treatment of Diabetes. J Diabetes Metab 4: 270. doi:10.4172/2155-6156.1000270

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 hydroxlase 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 hyperinsulinemic [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

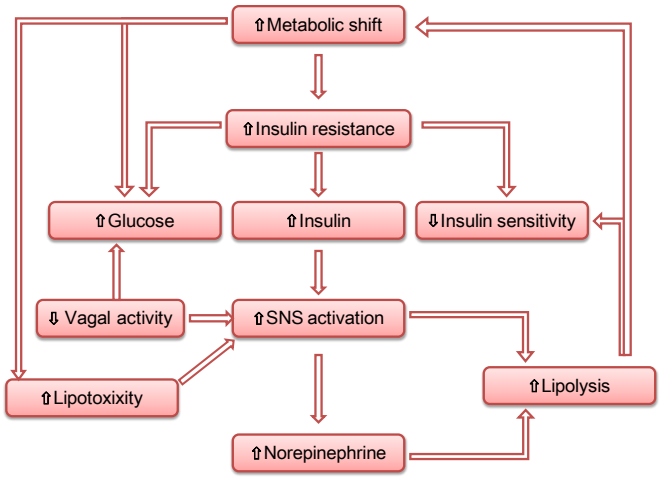

Figure 1: Reciprocity between the autonomic nervous system (ANS) and diabetes. Metabolic shift can increase blood glucose levels, insulin resistance and lipotoxicity. Increased blood glucose and increased insulin resistance lead to elevated insulin levels and insulin sensitivity, thus activating the SNS. As a result, norepinephrine release and lipolysis increase, further exacerbating metabolic shift and lowering insulin sensitivity. In retrospect, vagal impairment can lead to sympathetic overactivity as well as hyperglycemia.

regions of brain, including the rostral ventral lateral medulla (rVLM), hypothalamic arcuate nucleus (ARC), midbrain ventrolateral periaqueductal gray (vlPAG) nuclei, medullary nucleus raphé 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 vlPAG

Early studies suggested that EA attenuates the sympathoexcitatory reflex responses through the release of opioids, GABA, nociceptin and serotonin (or 5-hydroxytryptamine, 5-HT) 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.

Immunohistochemical staining studies have demonstrated the

presence of enkephalinergic 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 vlPAG 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 vlPAG [42].

Furthermore, EA, through presynaptic endocannabinoid CB1 receptor stimulation, reduces the vlPAG release of GABA but not glutamate during EA [43]. Reduced GABA disinhibits vlPAG 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 vlPAG 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 vlPAG 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 vlPAG responses to splanchnic nerve (SN) stimulation [37]. Additionally, EA increases SN-evoked discharge of vlPAG 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 vlPAG appear to be essential to the inhibitory influence of EA on the pressor reflex induced by SN and gallbladder afferent stimulation.

vlPAG-rVLM Projections

The vlPAG 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 vlPAG to the medulla have been documented in tract tracing studies [47]. However, a vlPAG projection to the raphé, in particular the nucleus raphé obscurus (NRO), also exists and has been thought to form an indirect pathway from the vlPAG 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 kyneurnic acid transiently reverses activation of neurons in the rVLM during stimulation of the vlPAG 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-HT_{1A} receptors in the rVLM complete the vlPAG-NRP-rVLM circuit to modulate cardiovascular activity [50]. Thus, an indirect connection from the vlPAG 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 vlPAG and the rVLM also might serve a functional role in EA-cardiovascular modulation. The direct or indirect projections from the vlPAG 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 vlPAG 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 vlPAG partially reverses rVLM neuronal responses and cardiovascular inhibition during DLH stimulation of the ARC. Conversely, depolarization blockade of the caudal vlPAG 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 vlPAG, particularly the caudal vlPAG, 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 *Zusanli* (*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. intermediolateral colum, 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 sympathoexcitation, 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, vlPAG 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.

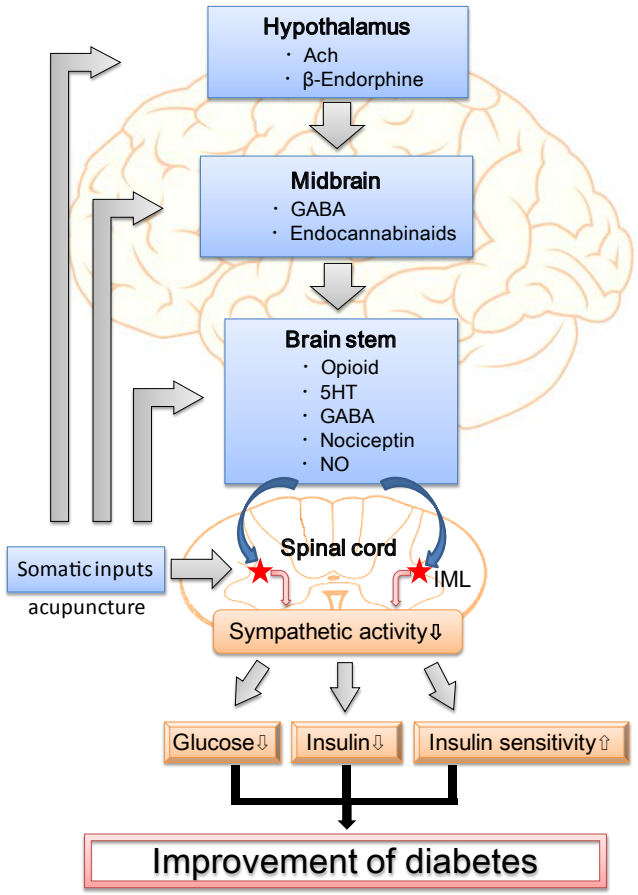

Figure 2: The putative neural mechanism of hypoglycemic response to acupuncture. Abbreviations: GABA: γ-Aminobutyric Acid; 5HT: 5-Hydroxytryptamine or Serotonin; NO: Nitric Oxide; IML: Intermediolateral Column of the Spinal Cord; DM: Diabetes Mellitus.

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

1. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF (2003) Lifetime risk for diabetes mellitus in the United States. JAMA 290: 1884-1890.
2. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, et al. (2007) Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 298: 309-316.
3. Berger M, Mühlhauser I (1999) Diabetes care and patient-oriented outcomes. JAMA 281: 1676-1678.
4. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A (2007) Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 298: 299-308.
5. Peplow PV, Baxter GD (2012) Electroacupuncture for control of blood glucose in diabetes: literature review. J Acupunct Meridian Stud 5: 1-10.
6. Zhou W, Longhurst JC (2006) Review of trials examining the use of acupuncture to treat hypertension. Future Cardiol 2: 287-292.
7. Zhou W, Longhurst JC (2012) Neuroendocrine mechanisms of acupuncture in the treatment of hypertension. Evid Based Complement Alternat Med 2012: 878673.
8. Tjen-A-Looi SC, Li P, Longhurst JC (2004) Medullary substrate and differential cardiovascular responses during stimulation of specific acupoints. Am J Physiol Regul Integr Comp Physiol 287: R852-862.
9. CabioÄŸlu MT, Ergene N (2006) Changes in levels of serum insulin, C-Peptide and glucose after electroacupuncture and diet therapy in obese women. Am J Chin Med 34: 367-376.
10. Szczudlik A, Lypka A (1984) Acupuncture-induced changes in human plasma insulin level. Acupunct Electrother Res 9: 1-9.
11. Chang SL, Lin KJ, Lin RT, Hung PH, Lin JG, et al. (2006) Enhanced insulin sensitivity using electroacupuncture on bilateral Zusanli acupoints (ST 36) in rats. Life Sci 79: 967-971.
12. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, et al. (2006) Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 47: 789-793.
13. Ishizaki N, Okushi N, Yano T, Yamamura Y (2009) Improvement in glucose tolerance as a result of enhanced insulin sensitivity during electroacupuncture in spontaneously diabetic Goto-Kakizaki rats. Metabolism 58: 1372-1378.
14. Pai HC, Tzeng CY, Lee YC, Chang CH, Lin JG, et al. (2009) Increase in plasma glucose lowering action of rosiglitazone by electroacupuncture at bilateral Zusanli acupoints (ST.36) in rats. J Acupunct Meridian Stud 2: 147-151.
15. Shapira MY, Appelbaum EY, Hirshberg B, Mizrahi Y, Bar-On H, et al. (2000) A sustained, non-insulin related, hypoglycaemic effect of electroacupuncture in diabetic Psammomys obesus. Diabetologia 43: 809-813.
16. Tseng CS, Shen WC, Cheng FC, Chen GW, Li TC, et al. (2005) Dynamic change in energy metabolism by electroacupuncture stimulation in rats. Am J Chin Med 33: 767-778.
17. Lin JG, Chen WC, Hsieh CL, Tsai CC, Cheng YW, et al. (2004) Multiple sources of endogenous opioid peptide involved in the hypoglycemic response to 15 Hz electroacupuncture at the Zhongwan acupoint in rats. Neurosci Lett 366: 39-42.

18. Masuo K, Rakugi H, Ogihara T, Esler MD, Lambert GW (2010) Cardiovascular and renal complications of type 2 diabetes in obesity: role of sympathetic nerve activity and insulin resistance. Curr Diabetes Rev 6: 58-67.

19. Perin PC, Maule S, Quadri R (2001) Sympathetic nervous system, diabetes, and hypertension. Clin Exp Hypertens 23: 45-55.

20. Thackeray JT, Radziuk J, Harper ME, Suuronen EJ, Ascah KJ, et al. (2011) Sympathetic nervous dysregulation in the absence of systolic left ventricular dysfunction in a rat model of insulin resistance with hyperglycemia. Cardiovasc Diabetol 10: 75.

21. Thackeray JT, Beanlands RS, Dasilva JN (2012) Altered sympathetic nervous system signaling in the diabetic heart: emerging targets for molecular imaging. Am J Nucl Med Mol Imaging 2: 314-334.

22. Carnethon MR, Craft LL (2008) Autonomic regulation of the association between exercise and diabetes. Exerc Sport Sci Rev 36: 12-18.

23. Carnethon MR, Jacobs DR Jr, Sidney S, Liu K; CARDIA study (2003) Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: the CARDIA study. Diabetes Care 26: 3035-3041.

24. Esler M (1995) Sympathetic nervous system: contribution to human hypertension and related cardiovascular diseases. J Cardiovasc Pharmacol 26: S24-28.

25. Esler M, Rumantir M, Kaye D, Lambert G (2001) The sympathetic neurobiology of essential hypertension: disparate influences of obesity, stress, and noradrenaline transporter dysfunction? Am J Hypertens 14: 139S-146S.

26. Troisi RJ, Weiss ST, Parker DR, Sparrow D, Young JB, et al. (1991) Relation of obesity and diet to sympathetic nervous system activity. Hypertension 17: 669-677.

27. Vinik AI, Ziegler D (2007) Diabetic cardiovascular autonomic neuropathy. Circulation 115: 387-397.

28. Vinik AI, Erbas T, Casellini CM (2013) Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig 4: 4-18.

29. Parati G, Esler M (2012) The human sympathetic nervous system: its relevance in hypertension and heart failure. Eur Heart J 33: 1058-1066.

30. Guyenet P (1990) Role of ventral medulla oblongata in blood pressure regulation, in Central regulation of autonomic functions, S.K. Loewy AD, Editor. Oxford University Press: 145-167.

31. Guertzenstein PG, Silver A (1974) Fall in blood pressure produced from discrete regions of the ventral surface of the medulla by glycine and lesions. J Physiol 242: 489-503.

32. Zhou WY, Tjen-A-Looi SC, Longhurst JC (2005) Brain stem mechanisms underlying acupuncture modality-related modulation of cardiovascular responses in rats. J Appl Physiol 99: 851-860.

33. Tjen-A-Looi SC, Li P, Longhurst JC (2003) Prolonged inhibition of rostral ventral lateral medullary premotor sympathetic neurons by electroacupuncture in cats. Auton Neurosci 106: 119-131.

34. Crisostomo MM, Li P, Tjen-A-Looi SC, Longhurst JC (2005) Nociceptin in rVLM mediates electroacupuncture inhibition of cardiovascular reflex excitatory response in rats. J Appl Physiol 98: 2056-2063.

35. Huangfu DH, Li P (1988) Role of nucleus raphe obscurus in the inhibition of defense reaction by deep peroneal nerve stimulation. Chin J Physiol Sci 4: 77-83.

36. Huangfu DH, Li P (1988) The inhibitory effect of ARC-PAG-NRO system on the ventrolateral medullary neurons in the rabbit. Chin J Physiol Sci 4: 115-125.

37. Li P, Tjen-A-Looi SC, Longhurst JC (2006) Excitatory projections from arcuate nucleus to ventrolateral periaqueductal gray in electroacupuncture inhibition of cardiovascular reflexes. Am J Physiol Heart Circ Physiol 290: H2535-2542.

38. Li P, Yao Y (1992) Mechanism of the modulatory effect of acupuncture on abnormal cardiovascular functions. Shanghai: Shanghai Medical University.

39. Guo ZL, Longhurst JC (2007) Expression of c-Fos in arcuate nucleus induced by electroacupuncture: relations to neurons containing opioids and glutamate. Brain Res 1166: 65-76.

40. Zhou W, Fu LW, Guo ZL, Longhurst JC (2007) Role of glutamate in the rostral ventrolateral medulla in acupuncture-related modulation of visceral reflex sympathoexcitation. Am J Physiol Heart Circ Physiol 292: H1868-1875.

41. Dampney RA, Fontes M, Hirooka Y, Horiuchi J, Potts PD, et al. (2002) Role of angiotensin II receptors in the regulation of vasomotor neurons in the ventrolateral medulla. Clin Exp Pharmacol Physiol 29: 467-472.

42. Dampney RA, Horiuchi J, Tagawa T, Fontes MA, Potts PD, et al. (2003) Medullary and supramedullary mechanisms regulating sympathetic vasomotor tone. Acta Physiol Scand 177: 209-218.

43. Fu LW, Longhurst JC (2009) Electroacupuncture modulates vlPAG release of GABA through presynaptic cannabinoid CB1 receptors. J Appl Physiol 106: 1800-1809.

44. Tjen-A-Looi SC, Li P, Longhurst JC (2009) Processing cardiovascular information in the vlPAG during electroacupuncture in rats: roles of endocannabinoids and GABA. J Appl Physiol 106: 1793-1799.

45. Li M, Tjen-A-Looi SC, Longhurst JC (2010) Electroacupuncture enhances preproenkephalin mRNA expression in rostral ventrolateral medulla of rats. Neurosci Lett 477: 61-65.

46. Tjen-A-Looi SC, Li P, Longhurst JC (2006) Midbrain vlPAG inhibits rVLM cardiovascular sympathoexcitatory responses during electroacupuncture. Am J Physiol Heart Circ Physiol 290: H2543-2553.

47. Loewy A (1990) Central autonomic pathways. Central Regulation of Autonomic Functions (ed. Loewy SK) Oxford University Press: New York. 88-103.

48. Li P, Tjen-A-Looi SC, Guo ZL, Fu LW, Longhurst JC (2009) Long-loop pathways in cardiovascular electroacupuncture responses. J Appl Physiol 106: 620-630.

49. Guo ZL, Moazzami AR, Tjen-A-Looi S, Longhurst JC (2008) Responses of opioid and serotonin containing medullary raphe neurons to electroacupuncture. Brain Res 1229: 125-136.

50. Li P, Tjen-A-Looi SC, Longhurst JC (2010) Nucleus raphe pallidus participates in midbrain-medullary cardiovascular sympathoinhibition during electroacupuncture. Am J Physiol Regul Integr Comp Physiol 299: R1369-1376.

51. Guo ZL, Moazzami AR, Longhurst JC (2004) Electroacupuncture induces c-Fos expression in the rostral ventrolateral medulla and periaqueductal gray in cats: relation to opioid containing neurons. Brain Res 1030: 103-115.

52. Li DP, Averill DB, Pan HL (2001) Differential roles for glutamate receptor subtypes within commissural NTS in cardiac-sympathetic reflex. Am J Physiol Regul Integr Comp Physiol 281: R935-943.

53. Longhurst JC (2003) Neural regulation of the cardiovascular system (2nd Edn) of Fundamental Neuroscience, S.E. al, Editor. Academic Press: San Diego: 935-966.

54. Lee JH, Beitz AJ (1992) Electroacupuncture modifies the expression of c-fos in the spinal cord induced by noxious stimulation. Brain Res 577: 80-91.

55. Lee JH, Beitz AJ (1993) The distribution of brain-stem and spinal cord nuclei associated with different frequencies of electroacupuncture analgesia. Pain 52: 11-28.

56. Dun NJ, Dun SL, Hwang LL (1997) Nociceptin-like immunoreactivity in autonomic nuclei of the rat spinal cord. Neurosci Lett 234: 95-98.

57. Quirion R (1984) Pain, nociception and spinal opioid receptors. Prog Neuropsychopharmacol Biol Psychiatry 8: 571-579.

58. Hofstetter CP, Card JP, Olson L (2005) A spinal cord pathway connecting primary afferents to the segmental sympathetic outflow system. Exp Neurol 194: 128-138.

59. Zhou Yi Syuu W, Hsiao I, Lin VW, Longhurst JC (2006) Modulation of cardiovascular excitatory responses in rats by transcutaneous magnetic stimulation: role of the spinal cord. J Appl Physiol 100: 926-932.

60. Zhou W, Mahajan A, Longhurst JC (2009) Spinal nociceptin mediates electroacupuncture-related modulation of visceral sympathoexcitatory reflex responses in rats. Am J Physiol Heart Circ Physiol 297: H859-865.

61. Han JS, Xie GX, Zhou ZF, Folkesson R, Terenius L (1982) Enkephalin and beta-endorphin as mediators of electro-acupuncture analgesia in rabbits: an antiserum microinjection study. Adv Biochem Psychopharmacol 33: 369-377.

62. Pomeranz B, Cheng R (1979) Suppression of noxious responses in single neurons of cat spinal cord by electroacupuncture and its reversal by the opiate antagonist naloxone. Exp Neurol 64: 327-341.

63. Wyszogrodski I, Polosa C (1973) The inhibition of sympathetic preganglionic neurons by somatic afferents. Can J Physiol Pharmacol 51: 29-38.

64. Chau D, Johns DG, Schramm LP (2000) Ongoing and stimulus-evoked activity of sympathetically correlated neurons in the intermediate zone and dorsal horn of acutely spinalized rats. J Neurophysiol 83: 2699-2707.

65. Deuchars SA (2007) Multi-tasking in the spinal cord--do 'sympathetic' interneurones work harder than we give them credit for? J Physiol 580(Pt.

66. Chang SL, Lin JG, Chi TC, Liu IM, Cheng JT (1999) An insulin-dependent hypoglycaemia induced by electroacupuncture at the Zhongwan (CV12) acupoint in diabetic rats. Diabetologia 42: 250-255.

67. Chang SL, Tsai CC, Lin JG, Hsieh CL, Lin RT, et al. (2005) Involvement of serotonin in the hypoglycemic response to 2 Hz electroacupuncture of zusanli acupoint (ST36) in rats. Neurosci Lett 379: 69-73.

68. Lee YC, Li TM, Tzeng CY, Chen YI, Ho WJ, et al. (2011) Electroacupuncture at the Zusanli (ST-36) Acupoint Induces a Hypoglycemic Effect by Stimulating the Cholinergic Nerve in a Rat Model of Streptozotocine-Induced Insulin-Dependent Diabetes Mellitus. Evid Based Complement Alternat Med: 650263.

69. Lee YC, Li TM, Tzeng CY, Cheng YW, Chen YI, et al. (2011) Electroacupuncture-induced cholinergic nerve activation enhances the hypoglycemic effect of exogenous insulin in a rat model of streptozotocin-induced diabetes. Exp Diabetes Res 2011: 947138.

70. Hamnvik OP, McMahon GT (2009) Balancing risk and benefit with oral hypoglycemic drugs. Mt Sinai J Med 76: 234-243.

71. Rizos CV, Elisaf MS, Mikhailidis DP, Liberopoulos EN (2009) How safe is the use of thiazolidinediones in clinical practice? Expert Opin Drug Saf 8: 15-32.

72. Chao M, Zou D, Zhang Y, Chen Y, Wang M, et al. (2009) Improving insulin resistance with traditional Chinese medicine in type 2 diabetic patients. Endocrine 36: 268-274.

73. Li YJ, Xu HX (2006) Research progress on anti-diabetic Chinese medicines. Zhong Yao Cai 29: 621-624.

This article was originally published in a special issue, **Diabetic Macrovascular Complications** handled by Editor(s). Dr. Judith Aponte, "Assistant Professor City University of New York, USA