Hypoglycemic effects and mechanisms of electroacupuncture on insulin resistance

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Yin J, Kuang J, Chandalia M, Tuvendorj D, Tumurbaatar B, Abate N, Chen JD. Hypoglycemic effects and mechanisms of electroacupuncture on insulin resistance. Am J Physiol Regul Integr Comp Physiol 307: R332–R339, 2014. First published May 21, 2014; doi:10.1152/ajpregu.00465.2013.—The aim of this study was to investigate effects and mechanisms of electroacupuncture (EA) on blood glucose and insulin sensitivity in mice fed a high-fat diet. Both wild-type (WT) and adipose ectonucleotide pyrophosphate phosphodiesterase (ENPP1) transgenic (TG) mice were fed a high-fat diet for 12 wk; for each mouse, an intraperitoneal glucose tolerance test (IPGTT) and insulin tolerance test (ITT) were performed with or without EA at abdomen or auricular areas. A high-fat diet-induced insulin resistance in both WT and TG mice. In the WT mice, EA at 3 Hz and 15 Hz, but not at 1 Hz or 100 Hz, via CV4+CV12 significantly reduced postprandial glucose levels; EA at 3 Hz was most potent. The glucose level was reduced by 61.7% at 60 min and 74.5% at 120 min with EA at 3 Hz (all P < 0.001 vs. control). Similar hypoglycemic effect was noted in the TG mice. On the contrary, EA at auricular points increased postprandial glucose level (P < 0.03). EA at 3 Hz via CV4+CV12 significantly enhanced the decrease of blood glucose after insulin injection, suggesting improvement of insulin sensitivity. Plasma free fatty acid was significantly reduced by 42.5% at 15 min and 50.8% at 30 min with EA (P < 0.01) in both WT and TG mice. EA improves glucose tolerance in both WT and TG mice fed a high-fat diet, and the effect is associated with stimulation parameters and acupoints and is probably attributed to the reduction of free fatty acid.

electroacupuncture; insulin resistance; glucose; vagal activity; free fatty acid

Diabetes affects about 8.3% of Americans with an estimated total cost of over $174 billion (3). In addition, about 79 million American adults have prediabetes (3) and about 34% of American adults have metabolic syndrome (14). Insulin resistance is one of the major contributing factors for diabetes, prediabetes, and metabolic syndrome. Obesity is virtually always associated with insulin resistance (16). Insulin resistance increases with weight gain and decreases with weight loss (44), indicating that fat accumulation is not only associated with but, in fact, causes insulin resistance (5). In addition, insulin resistance is known to be attributed to elevated plasma free fatty acid (FFA) (6). Elevated plasma FFA and intracellular lipid inhibit insulin signaling, leading to a reduction in insulin-stimulated muscle glucose transport (13, 27). The resulting suppression of muscle glucose transport leads to reduced muscle glycogen synthesis and glycosis.

Obese patients with insulin resistance have been reported to have increased adipose tissue ectonucleotide pyrophosphate phosphodiesterase (ENPP1) (17). ENPP1 modulates insulin action by physical interaction with the α-subunit of the insulin receptor and inhibition of β-subunit activation (20, 24, 36). In the transgenic model, previous studies elucidated that ENPP1 overexpression in insulin-sensitive tissues (liver, muscle, and brain) plays a role in insulin resistance and hyperglycemia, suggesting an important animal model to investigate insulin resistance. Recently, one study has shown that in the presence of a high-fat diet, transgenic model with ENPP1 overexpression in adipocytes induces fatty liver, hyperlipidemia, and dysglycemia, recapitulating key manifestation of the metabolic syndrome (41).

Acupuncture has been shown to be effective in treating patients with diabetes and seems more effective in treating Type 2 diabetes than Type 1 diabetes (23). Patients with diabetes treated with acupuncture showed improved clinical manifestation, as well as reduction in fasting blood glucose and improvement in oral glucose tolerance. Other studies indicated that acupuncture improved both hyperglycemia and insulin resistance (11, 15). In animals, electroacupuncture (EA) has been shown to improve insulin resistance or sensitivity (10, 25, 26, 31, 37) and reduce plasma FFA (32). In the current study, we hypothesized that EA reduces elevated blood glucose level in a mouse model of insulin resistance, and the mechanism may be via the suppression of FFA.

Our aims of this study were, therefore, to investigate the effects and mechanisms of EA on blood glucose and insulin sensitivity in regular mice fed a high-fat diet and ENPP1 transgenic mice fed a high-fat diet. The experiments were designed to study the effects of EA on glucose tolerance, insulin tolerance, and plasma insulin, as well as mechanisms involving FFA.

MATERIALS AND METHODS

Subjects

Thirty-two female wild-type (WT; C57BL/6j) mice and 16 female transgenic (TG) mice were used in the study. The transgenic mice were produced by the Department of Endocrinology, University of Texas Medical Branch in Galveston, TX. The breeding method was established in Dr. Abate’s laboratory and has been previously published (41). The mice were housed in the microisolator cage equipped...
with filter hoods under controlled temperature (20°C) and with a 12:12-h light-dark cycle and free access to water and solid food. The experimental protocol was approved by the Institutional Animal Care and Use Committee, University of Texas Medical Branch at Galveston, Texas.

**Diet**

The “ad libitum” diet was started at 8 wk of age in both WT and TG mice, and the animals had free access to high-fat chow (60% fat by calories; Research Diets D12492, New Brunswick, NJ). For the paired-feeding WT group, each animal was given the same amount of high-fat chow consumed by the corresponding paired transgenic mouse the day before. The experiments were initiated after 12 wk of feeding.

**Electroacupuncture**

The study was conducted under anesthesia (inhalation of isoflurane 1.5–2%) after the mouse was fasted for 5 h. Electroacupuncture was performed either in the abdominal acupoints CV4 and CV12 or bilateral auricular acupoints. CV4 (Guanyuan) is located at 2 units above the upper crest of pubis bone (total 14 units from pubis bone to the top of xiphoid process), while CV12 (Zhongwan) is located at seven units above CV4 (9, 30). The ear acupoints are located around auricular concha bilaterally. In the abdominal EA, the positive charge was introduced at CV4, and the negative charge was connected to CV12. The needles (short and tiny needles used for auricular acupuncture in clinics. 0.22 × 1.8 mm; UPC Medical Supplies, San Gabriel, CA) were inserted into the acupoints with the depth of 0.5–1 mm and connected an electrostimulator (PulseMaster A300, World Precision Instruments, Sarasota FL) (Fig. 1). Stimulation parameters were set at continuous on, pulse width of 0.5 ms, various pulse frequency of 1 Hz, 3 Hz, 15 Hz, or 100 Hz and amplitude of 4 mA (abdominal EA) or 1 mA (auricular EA).

**Experimental Protocol**

**Experiment 1: diet on glucose tolerance.** Four groups of mice (n = 8 in each group) were used in this experiment: 1) WT mice fed a regular chow ad libitum diet; 2) WT mice fed a high-fat diet ad libitum; and 3) paired feeding groups of WT and TG mice fed a high-fat diet. The pairing was decided by body weight and age. The intraperitoneal glucose tolerance test (IPGTT) was performed after 5 h of fasting by intraperitoneal injection of 20% glucose (1 g/kg body wt). About a 5-μl blood sample was then collected from the tail vein at each time point 0 (baseline) and then 15, 30, 60, 90, and 120 min after the injection for the assessment of blood glucose level. The blood glucose level was measured by a glucometer (Accu-Check Aviva, Roche, Mannheim, Germany). No stimulation was performed in the experiment.

**Experiment 2: EA on glucose tolerance with various parameters.** Eight WT mice were used in this experiment. Each mouse was studied in five sessions in a randomized order: control without stimulation, EA-1 Hz, EA-3 Hz, EA-15 Hz, and EA-100 Hz. The IPGTT was performed in each session as described in experiment 1. Abdominal EA at CV4+CV12 was performed during the entire 120-min period. This is a pilot study, and we didn’t know which time point the hypoglycemic effect of EA would occur; therefore, we chose to perform EA through the entire 120-min OGTT study, which is similar to a study previously reported (25).

**Experiment 3: EA on glucose tolerance with various stimulating locations.** Both WT and TG mice were used in the experiment (n = 8 in each group). Each mouse was studied in three randomized sessions: control without stimulation, EA-3 Hz at the abdominal location CV4+CV12, and EA-3 Hz at the auricular location. The 3 Hz was chosen because it yielded best hypoglycemic effect based on the preliminary results from the experiment 1. After a 5-h fast, IPGTT was performed as described in the experiment 1. In addition to the tail blood sample taken from each time point for glucose measurement, 30–40-μl blood samples were collected from the tail at 0, 15, 60, and 90 min after the glucose injection for the assessment of plasma insulin level. EA was performed during the entire experimental period.

**Experiment 4: EA on insulin sensitivity.** Six WT mice and six TG mice from the experiments 1 and 2 were used in this experiment. Each mouse was studied in two sessions randomly: control without stimulation and EA-3 Hz at CV4+CV12. Insulin tolerance test (ITT) was performed after the mice were fasted for 5 h. Regular insulin (Humulin U-100; Lilly, Indianapolis, IN) in a saline solution (0.5 U/kg) was injected to the intraperitoneal cavity. A sample drop of blood (less than 5 μl) was then collected from the tail vein at the following time points: 0 (baseline) and 15, 30, 60, 90, and 120 min for the assessment of glucose level (Accu-Check Aviva, Roche). In addition, 30–40-μl blood samples were collected during the test at three time points: baseline, 15, and 30 min for measuring plasma free fatty acid level. Abdominal EA was performed for 120 min.

**Analysis of Peptides**

Blood samples were collected in chilled EDTA tubes (Microvette CB300, Sarstedt, Germany) and then centrifuged at 4°C at 3,000 rpm speed for 30 min. Plasma was obtained and stored at −80°C. Insulin was assayed using Ultra Sensitive Mouse Insulin ELISA kit (catalog no. 90080; Crystal Chem). FFA was assayed using nonesterified fatty acids detection ELISA kit (catalog no. SFA-1; Zen-Bio, Durham, NC).

**Statistical Analysis**

Data are presented as means ± SE. One-way ANOVA was used for multiple comparisons, such as different diets, different parameters, or locations. A two-tailed Student t-test was used for comparison between control and EA. In the insulin tolerance test, the percentage of glucose change compared with the baseline at each time point was used to represent the insulin sensitivity. Significance was defined as P < 0.05.
RESULTS

High-Fat Diet and Glucose Tolerance

The regular chow had no effects on glucose tolerance. As shown in Fig. 2, the peak blood glucose level in the WT mice with “ad libitum” regular chow feeding was at 60 min (356.0 ± 16.6 mg/dl) and back to the baseline after 120 min (220.1 ± 17.2 mg/dl).

However, the high-fat diet induced glucose tolerance in all three groups of rats: the ad libitum group and the paired feeding WT and TG groups. In the ad libitum regular mice fed a high-fat diet, the blood glucose level after glucose injection was 491.7 ± 21.9 mg/dl at 60 min and was sustained at 456.7 ± 28.1 mg/dl at 120 min, these were significantly higher than those in the regular chow group (P < 0.001). The same findings were observed in the paired feeding WT and TG groups; the blood glucose levels in the paired feeding WT and TG group was also high and even higher than the WT ad libitum high-fat diet group at certain points. As shown in Fig. 1, at 120 min, the blood glucose level was 576.8 ± 23.3 mg/dl in the WT paired group (P = 0.02 vs. WT ad libitum high-fat diet group) and 558.5 ± 21.6 mg/dl in the TG-paired group (P = 0.01 vs. WT ad libitum high-fat diet group).

Parameter-Dependent Effects of EA on Postprandial Glycemic Control

EA at 3 Hz and 15 Hz significantly reduced postprandial blood glucose level from 30 min to 120 min, and 3 Hz was more potent than 15 Hz. The postprandial blood glucose level was substantially reduced from 396.9 ± 9.7 mg/dl in the control session to 281.9 ± 36.1 mg/dl with EA-3 Hz at 30 min (P < 0.01), from 436.8 ± 26.2 mg/dl to 167.1 ± 28.1 mg/dl at 60 min (P < 0.001) and from 300.0 ± 55.8 mg/dl to 76.5 ± 18.1 mg/dl at 120 min (P < 0.01) (Fig. 3).

However, neither EA at 1 Hz nor EA at 100 Hz reduced postprandial blood glucose during the entire 120-min experimental period. At 120 min, EA at both 1 Hz and 100 Hz actually increased blood glucose level; it was 410.5 ± 55.8 mg/dl in the EA-1 Hz session (P = 0.02 vs. control) and 476.2 ± 44.7 mg/dl in the EA-100-Hz session (P = 0.001 vs. control; Fig. 3).

Location-Dependent Effects of EA on Postprandial Glycemic Control

In the wild-type mice, EA with 3 Hz at abdominal location CV4 and CV12 significantly reduced the postprandial blood glucose level at 30, 60, 90, and 120 min; the blood glucose level was reduced by 29.0% at 30 min, 61.8% at 60 min, 71.0% at 90 min, and 74.5% at 120 min (all points, P < 0.01 vs. control). In contrast, EA with 3 Hz at the ear location increased the postprandial blood glucose level from 60 to 120 min. The blood glucose level was increased by 17.5% at 60 min, by 37.4% at 90 min, and by 72.5% at 120 min (all points, P < 0.03 vs. control). Fig. 4A, suggesting the opposite effect of EA at different locations on the blood glucose level.

Similar findings were observed in the TG mice. EA at CV4+CV12 significantly decreased the postprandial blood glucose level from 15 min to 120 min. As shown in Fig. 4B, EA at CV4+CV12 reduced blood glucose level from 364.1 ± 12.7 mg/dl to 303.0 ± 23.3 mg/dl at 15 min (P < 0.01), from 489.1 ± 42.1 mg/dl to 276.1 ± 37.5 mg/dl at 60 min (P < 0.01) and from 399.7 ± 56.6 mg/dl to 193.6 ± 59.6 mg/dl at 120 min (P = 0.04). EA at the ear location significantly increased glucose level to 512.2 ± 38.8 mg/dl at 120 min (P < 0.002 vs. control, Fig. 4B).

EA on Insulin Sensitivity

In the WT mice, abdominal EA significantly increased insulin sensitivity represented by an enhanced decrease of blood glucose in the insulin sensitivity test (Fig. 5A). It has to be mentioned that the blood glucose level decreases after the injection of insulin; therefore, the percentages of glucose change were shown as negative values starting from 15 min after insulin injection. The percentage of blood glucose from baseline (before insulin injection) was substantially decreased from 18.5 ± 5.4% in the control session to 49.7 ± 6.5% with EA at 30 min (P < 0.001), from 34.7 ± 6.6% to 69.2 ± 8.3% at 60 min (P = 0.0069 vs. control), and from 33.7 ± 10.4 to 80.1 ± 4.4% at 120 min (P = 0.01 vs. control).

Similar findings were observed in the TG mice. EA significantly decreased the percentage of blood glucose change from baseline from 30 min to 120 min after insulin injection (all P < 0.01 vs. control), suggesting an increase of insulin sensitivity with EA-3 Hz at the abdominal location (Fig. 5B).
EA on Plasma Insulin and Free Fatty Acid

EA-3 Hz at the abdominal locations significantly reduced plasma insulin level in both WT mice and TG mice (Fig. 6). In the WT mice, the plasma insulin level was reduced from 0.8 ± 0.2 ng/ml in the control session to 0.5 ± 0.03 ng/ml with EA at 15 min (P = 0.046; Fig. 6A); from 1.3 ± 0.2 ng/ml to 0.6 ± 0.2 ng/ml at 90 min (P = 0.006 vs. control). In the TG mice, EA showed similar results; however, the significance was only observed at 90 min (P = 0.01 vs. control, Fig. 6B).

EA substantially suppressed plasma FFA in both WT and TG mice (Fig. 7). In the WT mice, the plasma FFA level was reduced from 91.2 ± 10.6 ng/ml in the control session to 52.4 ± 3.7 with EA at 15 min (P = 0.005) and from 90.7 ± 10.4 ng/ml to 44.6 ± 4.2 ng/dl at 30 min (P = 0.004; Fig. 7A). Similar findings were observed in the TG mice (P = 0.009 vs. control at 15 min, P = 0.01 vs. control at 30 min, Fig. 7B).

DISCUSSION

In the current study, we have found that EA at frequencies of 3 Hz and 15 Hz at acupoints CV4 and CV12 significantly reduced blood glucose, increased insulin sensitivity, reduced plasma insulin, and suppressed plasma FFA in mice with high-fat diet-induced insulin resistance, suggesting the hypoglycemic effect of EA for insulin resistance.

Two murine models of insulin resistance were used in this study: regular mice with high-fat-induced insulin resistance and TG mice with ENPP1 overexpression. It was reported that adipose ENPP1-TG and WT littermates had similar body weights after being fed for 16 wk a regular chow diet; however, when exposed to high-fat diet, WT mice consumed more food and gained more weight than the transgenic mice (41). Our data indicated that with either free feeding or paired feeding, high-fat diet (60%) induced hyperglycemia and glucose intolerance in both WT and TG mice. The results of our study demonstrated similar hypoglycemic effects of EA on both TG mice and WT mice with high-fat diet-induced insulin resistance.

Low-frequency EA is applied more frequently for the treatment of insulin resistance with beneficial results (25, 29, 30). In the current study, we tested various frequencies and found EA with 3 Hz and 15 Hz reduced blood glucose; whereas neither 1 Hz nor 100 Hz had any hypoglycemic effect in mice. In general, low frequency is defined as below 4 Hz, and high frequency is defined as above 100 Hz. In a chart with a log scale, 15 Hz is in the middle point (21). Previous studies have shown EA at CV4 and CV12 with 15 Hz reduced plasma glucose concentration in rats with or without hyperglycemia (9); using the same EA method, Ishizaki et al. (25) reported glucose tolerance was improved and insulin sensitivity was enhanced during EA in diabetic Goto-Kakizaki rats. With 3 Hz EA at CV4 and ST36, Liang et al. (30) reported a reduction of fasting blood glucose after 8 wk of treatment in obese diabetic...
mice, an effect mediated via improvement in insulin sensitivity. Our findings were consistent with findings reported in the literature; however, we explored EA at more frequencies and different locations. We found that EA at both 15 Hz and 3 Hz improved glucose tolerance, and 3 Hz was more effective. In the current study, we also tried EA with 1 Hz and 100 Hz. Sixty minutes after EA at 1 Hz, there was a trend of decrease in blood glucose, but it was not significant; however, during the second 60 min, this minor hypoglycemic effect disappeared, and instead, a trend of an increase of blood glucose was observed. Our data at 100 Hz confirmed the ineffectiveness of EA with high frequency on blood glucose and insulin sensitivity. During 90–120 min IPGTT test, we noted an increase of blood glucose. It is interesting that both 1 Hz and 100 Hz increased blood glucose during the 90–120 min in the current study; however, both changes were statistically not significant. Because of the limitation in the total number of sessions we could perform in the same group of animals, we did not study the effect of EA at 2 Hz; however, on the basis of our data on 3-Hz EA and other studies (21), we would speculate a hypoglycemic effect with reduced potency on EA at 2 Hz.

The underlying mechanisms involved in the hypoglycemic effect of EA are not clear. Previous studies have shown EA at different frequencies releases different kinds of neuropeptides. For example, EA of 2 Hz accelerates the release of enkephalin, β-endorphin, and endomorphin, while that of 100 Hz selectively increases the release of dynorphin (21, 22). Increased β-endorphin was associated with decreased plasma glucose. In obese Zucker rats, an increase of plasma β-endorphin-like immunoreactivity was obtained in parallel with the reduction of plasma glucose (46). In an earlier study, Chang et al. (9) indicated that EA stimulation at CV12 could induce the secretion of β-endorphin to produce hypoglycemia in an insulin-dependent manner in rats. Another study demonstrated that serotonin may activate the 5-HT7 receptor in the rat adrenal gland to enhance β-endorphin secretion and then stimulates the opioid receptor to increase peripheral glucose utilization, resulting in decreased plasma glucose level in streptozotocin-diabetic rats (12). In the present study, we believe that low-frequency, but not high-frequency, EA accelerated the release of β-endorphin, which further decreased the glucose tolerance in insulin-resistant mice.

Autonomic nervous system dysfunction in terms of either an overactivation of sympathetic activity or a blunted vagal/parasympathetic activity has been shown to be associated with insulin resistance or diabetes (8, 19, 33, 39, 43). In obese patients, increased visceral fat was reported to be associated with sympathetic overactivity and insulin resistance (29). Chronic sympathetic overactivity decreases insulin sensitivity. EA has been frequently and consistently shown to improve vagal activity and suppress sympathetic activity. EA reduced high sympathetic nerve activity in women with polycystic ovary syndrome (45). In animal models and humans with gastrointestinal motility disorders, EA was shown to increase vagal activity and reduce sympathovagal balance (34, 40, 48). On the basis of these previous findings, a possible autonomic mechanism is hypothesized: EA improves vagal activity and suppresses sympathetic activity, leading to a reduction in free fatty acid and improvement in insulin sensitivity. Although no direct
evidence was available to support such a hypothesis, our data from the insulin tolerance test did demonstrate increased insulin sensitivity with EA. There is a close relation between the peripheral insulin sensitivity and insulin secretion because subjects with low insulin sensitivity or insulin resistance are adapted to secrete more insulin (1, 4, 28). Evidence has shown that increased cholinergic activation is involved in this adaptation. It was reported that cholinergic activation by carbachol returned insulin secretion and glucose intolerance to normal in insulin-resistant mice fed a high-fat diet (2). On the basis of these previous studies, the current findings are understandable: 3 Hz EA increased insulin sensitivity, yielding a reduced demand for amount of insulin, resulting in a reduced secretion in insulin that was originally elevated in insulin-resistant mice fed a high-fat diet, especially in the TG mice (41).

Impaired autonomic nervous system in insulin resistance contributes to the pathogenesis through an increase in lipolysis from adipose tissue and increase in plasma FFA (38, 47). In Type 2 diabetic patients, an increased postprandial plasma FFA concentration was found to be associated with increased sympathovagal balance (38). Sympathetic overactivity is believed to result in increased plasma FFA; the receptor has been found to play a crucial role in catecholamine-induced rate of FFA mobilization from mental fat cells (35). Increased fatty acid flux from adipose to peripheral circulation is known to reduce glucose utilization in skeletal muscle and increase triglyceride deposition in the liver (6). Increasing vago- nal or reducing sympathetic tone would, therefore, have a positive effect on fatty acid metabolism. Reduced fatty acid flux from the adipose tissue would improve insulin-mediated peripheral glucose utilization, mainly occurring in skeletal muscle, and reduce fatty infiltration of the liver. In the current study, we found 3-Hz abdominal EA reduced plasma FFA concentration in mice with insulin resistance, and this reduction was believed to play a major role in the improvement of glucose tolerance. Since there is a close relation between FFA and sympathetic activity, we believe the suppression of FFA is considered to be related to the decrease of sympathetic activity and to the improvement of insulin sensitivity.

Surprisingly, but interestingly, the hypoglycemic effect of EA was observed only at the abdominal locations but not at the auricular location. The points that we stimulated at the auricular area were considered to receive innervations from the auricular branch of vagus nerve (18, 42). Electrical activation of the vagus nerve was shown to stimulate insulin secretion both in vivo and in vitro in several different species, including humans (1, 7). In the literature, little has been reported on auricular acupuncture for treating diabetes, we hypothesized that similar to abdominal EA, by stimulating the auricular branch of the vagus, vagal activity might be increased and sympathetic activity might, thereby, be reduced so that insulin resistance could be improved. However, our results on auricular acupuncture failed to confirm such a hypothesis. This might be attributed to 1) in addition to the auricular branch of the vagus nerve, other sensory nerves innervating the ear may also be involved; and 2) low-frequency and low-energy stimulation was applied in the current study, which might not enhance vagal activity. In the literature, it was reported that strong or even painful stimulation was required to produce an autonomic response with auricular acupuncture (18). Surprisingly, our data indicated a trend of increasing blood glucose during auricular EA, implying that it may even cause hyperglycemia. Studies on auricular EA and glucose metabolism are required in future investigations.

The weakness of the study is the lack of chronic data. However, a positive chronic and sustained effect is speculated. Although not investigated in the present study, EA has been shown to have sustained effects in other studies; for example, the liquid/solid gastric emptying was continuously accelerated after the termination of EA (40, 49). Different from most of the other methods of electrical stimulation, such as cardiac stimulation and spinal cord stimulation with which stimulation has to be performed continuously, EA is typically performed once a day or a few times a day. This practice also implicitly suggests sustained effects of EA. Further studies are being performed in our laboratory to study the hypoglycemic effect of chronic EA.

Perspectives and Significance

Diabetes, prediabetes, and metabolic syndrome are common in the general population. Therefore, it is of great clinical significance to develop new therapies for these disorders. While acupuncture or EA has been shown to improve insulin resistance and effective in treating diabetes in some studies, its clinical application has not been popularized due to the limitation of study design, inconsistency of acupuncture locations, and parameters. In the current study, we have investigated the effects of EA on hyperglycemia in mouse models of insulin resistance, and various parameters and locations have been tested. We found EA at low frequency substantially improved glucose intolerance and increased insulin sensitivity by suppressing FFA, possibly attributed to the activation of vagal activity and/or the suppression of sympathetic activity. This pilot study provides important information in the development of an alternative therapy for prediabetes or diabetes. Future chronic study with low-frequency EA at abdominal locations should be performed to access the therapeutic potential of EA for insulin resistance and diabetes.

In conclusion, acute 3-Hz EA at abdominal points CV4 and CV12 exerts a hypoglycemic effect in both wild-type mice and ENPP1 TG mice with insulin resistance. The inhibitory effect of EA is attributed to an increase in insulin sensitivity at least partially mediated via the inhibition of FFA. EA applied at low frequency at CV4 and CV12 may have a therapeutic potential for diabetes; however, chronic studies are needed.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: J.Y., N.A., and J.D.C. conception and design of research; J.Y. and J.K. performed experiments; J.Y. and J.K. analyzed data; J.Y., M.C., D.T., B.T., N.A., and J.D.C. interpreted results of experiments; J.Y. prepared figures; J.Y. drafted manuscript; J.Y., M.C., N.A., and J.D.C. edited and revised manuscript; J.Y., N.A., and J.D.C. approved final version of manuscript.

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