IJPSR (2020), Volume 11, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 December 2019; received in revised form, 10 April 2020; accepted, 23 November 2020; published 01 December 2020

THE ROLE OF β-ENDORPHIN AND C-PEPTIDE IN STREPTOZOTOCIN INDUCED DIABETIC RATS WITH EFFECT OF ACU-TENS AT ZUSANLI (ST36) ACUPOINTS

R. Subbulakshmi [*1] and Girija Sivakumar [2]

Department of Anatomy [1], Vivekanandha Dental College for Women, Tiruchengode, Namakkal - 637205, Tamil Nadu, India.
Department of Anatomy [2], Karpaga Vinayaga Institute of Medical Sciences, Maduranthagam, Chennai - 603308, Tamil Nadu, India.

Keywords:

Zusanli (ST36), Acupoint, Streptozotocin, Diabetes, Acu-TENS, β-endorphin

Correspondence to Author:
R. Subbulakshmi

Professor,
Department of Anatomy,
Vivekanandha Dental College for Women, Tiruchengode, Namakkal - 637205, Tamil Nadu, India.

E-mail: ursubbulakshmi@rediffmail.com

ABSTRACT: Streptozotocin is 2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose drug is commonly used to induce diabetes in experimental rats. This study was designed to evaluate the role of β-endorphin and C-peptide in Acu-TENS therapy at Zusanli (ST36) acupoint. Diabetic was induced by Streptozotocin (45mg/kg/body weight) with a single dose of intraperitoneal injection in male albino Wistar rats. The diabetic rats were treated with Acu-TENS electrical stimulation with a pulsed current of low frequency and high intensity at bilateral Zusanli (ST36) acupoint without anesthesia for 60 days, and the effect was compared with pioglitazone (7.5 mg/kg/body weight) treated diabetic rats on fasting blood glucose, β-endorphin & C-peptide levels. The results showed that a significant reduction ($p \geq 0.01$) in fasting blood glucose and increased β-endorphin and C-peptide level in Zusanli (ST36) acupoint treated diabetic rats. The anti-diabetic effect of Zusanli (ST36) acupoint may be due to stimulation of Qi (life energy) and regulating the circulation of blood and an increase in insulin secretion through the mediation of β- endorphin.

INTRODUCTION: 'Streptozotocin is a glucos-amine-nitrosourea compound, and alkylating agent that damages DNA and is particularly toxic to pancreatic beta cells is widely used to induce experimental diabetic animal models' [1]. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia (elevated blood glucose) with abnormalities of carbohydrates, protein, and fat metabolism due to absolute or relative deficiency of insulin secretion and varying degrees of insulin resistance.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(12).6532-38

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(12).6532-38

The long term complications of diabetes lead to diseases of large blood vessels (macrovascular disease including coronary heart disease and peripheral arterial disease) and small blood vessels (microvascular disease, including retinal and renal vascular disease) [2]. Diabetes is a significant and growing threat to global health [3]. The global prevalence of diabetes as in 2016, 422 million people have diabetes worldwide, and the number of people with diabetes will expect to rise up to 592 million by 2035 [4]. In India, diabetes is gaining the status of a potential epidemic disease [5, 6] and becoming the diabetes capital of the World with a projected 109 million people with diabetes by 2035 [7]. Type 2 diabetes (NIDDM) is a common type of diabetes, adult-onset with the age group of > 40 years, occurs due to the combination of insulin resistance and reduced insulin secretion.

Obesity and physical inactivity are the leading risk factors for type 2 diabetes. Though medical treatment is convenient and effective, certain treatments can lead to serious adverse effects and are not always satisfactory in treating and preventing the long-term complications of diabetes [8, 9]. Patients with poorly controlled type 2 diabetes (non-insulin-dependent diabetes) who frequently use oral hypoglycemic agents often present with unstable glucose levels [10]. Increasing evidence suggests that C-peptide may be useful in predicting future levels of glycemic control, response to hypoglycemic agents, and risk of future diabetes complications. C-peptide and insulin are synthesized as a single polypeptide chain called proinsulin in the beta cells of pancreatic islet. Proinsulin cleaved and formed equal amounts of insulin and C-peptide, both entered the portal vein [11]. The great interest in C-peptide is due to the limitations of the use of serum insulin as a measure of insulin secretion because insulin, after its secretion into the portal vein, passes through the liver where approximately 50% of the delivered insulin is extracted [12]. Within the physiologic range of insulin concentrations, there is a variable fraction of hormone extracted by the liver. Peripheral insulin concentration therefore is the post hepatic insulin delivery rather than the secreted insulin by the pancreatic beta cells [12]. The measurement of C-peptide, which is co-secreted with insulin from beta cells of the pancreas, thus provides a better index of endogenous insulin production and pancreatic beta-cell function than insulin measurements [13].

In recent years, with the advancement of medicine and treatments, alternative therapies like acupuncture therapy, herbal medicine, dietary supplementation, yoga therapy, and hot tub therapy have become increasingly popular due to less adverse effects for treating diabetes. Acupuncture therapy, one of the oldest and most commonly used forms of alternative medicine, has existed for more than 2500 years. Various methods like exercise, diet control, and medication are also included for controlling blood glucose levels in patients with diabetes mellitus. Researchers have, therefore, searched for alternative or complementary treatment methods with no side effects to increase insulin sensitivity [14-17]. The effectiveness of acupuncture in diabetes had observed both in reducing the symptoms and preventing the long-term complications of diabetes. The effects of acupuncture on diabetes have been observed both experimentally and clinically [18]. Acupuncture can act on the pancreas to enhance insulin synthesis, increase the number of receptors on target cells, and accelerate the utilization of glucose, resulting in the lowering of blood sugar [19]. Various studies have shown the beneficial effect of acupuncture on obesity, which is the most modifiable risk factor for type 2 diabetes. The therapeutic effect of acupuncture on diabetes is mainly based on the action on multiple systems [20]. Nowadays, electro-acupuncture has been a growing interest in the glucose-lowering effect.

In our study, Zusanli (ST36) acupoint electric stimulation was selected for the treatment of diabetes based on traditional Chinese medicine[21]. The release of β-endorphin lowers the plasma glucose levels has been demonstrated by electro-acupuncture at the Zusanli acupoints in rats [22]. Endorphins (endogenous morphine) are endogenous opioid neuropeptides and peptide hormones. They are produced by CNS, pituitary gland, and endocrine pancreas [23]. Endorphins, a multi-functional chemical, are emitted to counteract and deal with sensations by transmitting electrical impulses through the body to the nervous system. Acupuncture therapy and meditation stimulates the release of endorphin. Beta-endorphin acts as a stimulant for an appetite that helps in the release of insulin from the beta cells of pancreas. Reid RL, in his study, explained the effect of beta-endorphin (2.5 mg IV bolus) to type 2 DM patients, showed a progressive decrease in plasma glucose [24]. The lowering in plasma glucose action in diabetes is believed to involve the promotion of β- endorphin secretion of insulin [15]. Electro-acupuncture (EA) is commonly used to stimulate the acupoints, an invasive technique with a needle than manually.

In this study, Transcutaneous electric nerve stimulation at acupoints (Acu-TENS) therapy, a non-invasive method, was selected to stimulate the acupoints, which combines the advantages of both electrical stimulation and acupuncture therapy. The application of acupuncture stimulation facilitates the local circulation system. It enhances glucose levels in serum, and these effects may be comparable to those produced as a result of physical exercise [15].

In this study, we aimed to investigate the effects of Zusanli acupoints stimulation with Acu-TENS (15Hz) on levels of fasting blood glucose, C-peptide, and β-endorphin in diabetic rats.

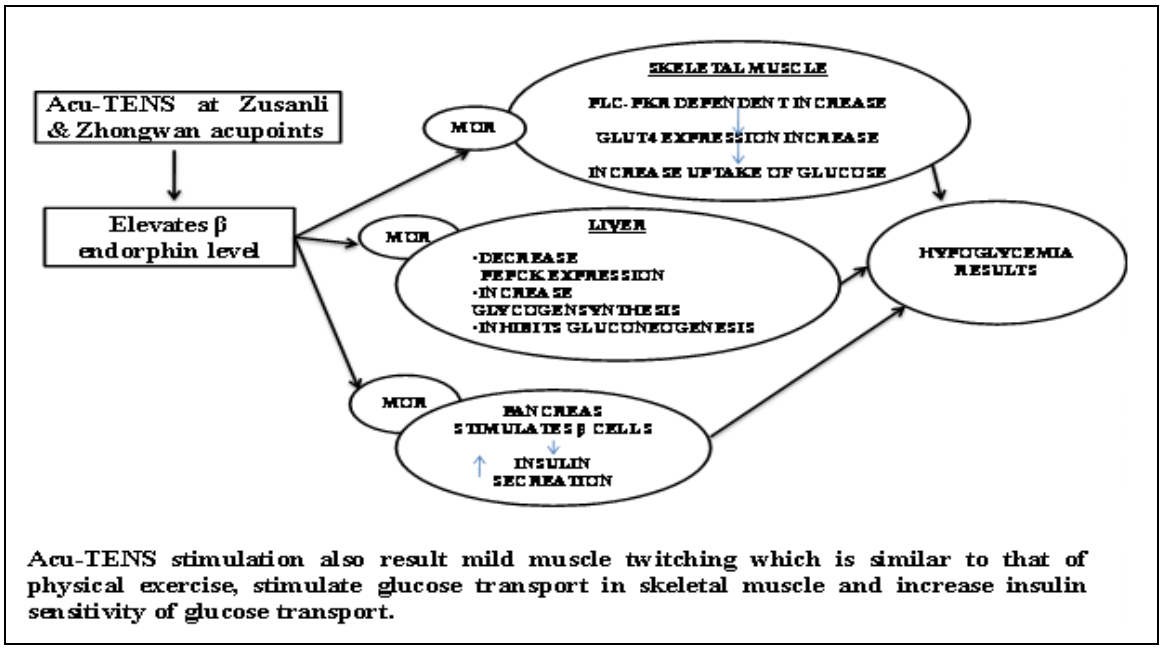


FIG. 1: POSSIBLE MECHANISM WITH ACU-TENS STIMULATION AT ACUPOINTS

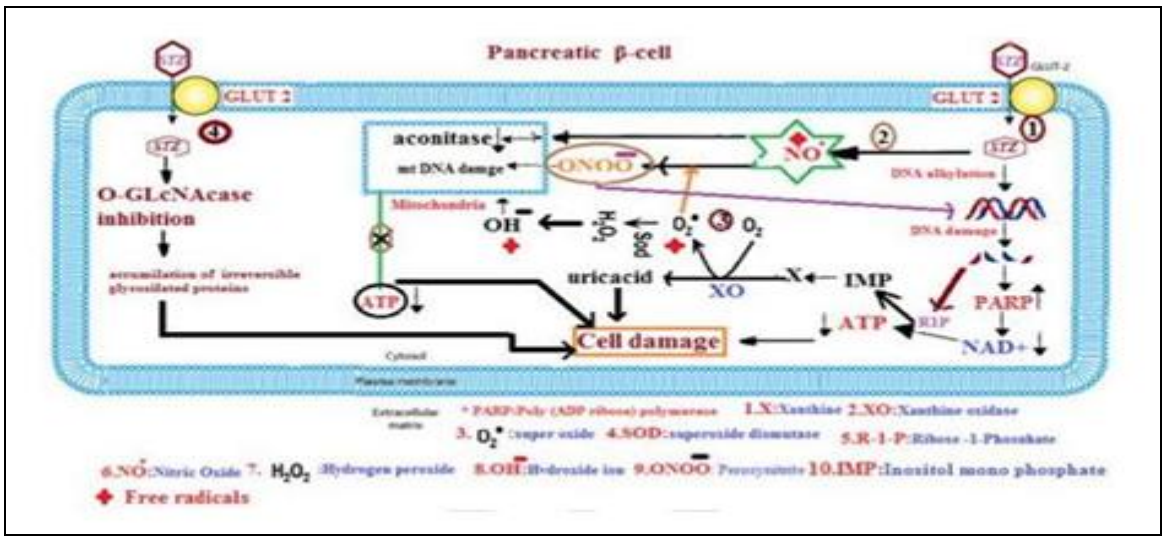


FIG. 2: STREPTOZOTOCIN - MODE OF ACTION

MATERIALS AND METHODS:

Experimental Animals: Male Wistar rats with a weight of 200-250gms were selected for this study. The experimental animals were kept well ventilated and maintained at controlled temperatures with 12 hours of light and dark cycles. Animals are given with standard laboratory diet and water ad libitum. The animal experiment was carried out as per CPCSEA guideline, and this study was approved by the Institutional Animal Ethical Committee (Reg. no. 889/PO/Re/S/05/CPCSEA/2018) of Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode.

Experimental Groups: Four groups with six animals in each were divided.

Group 1: Rats were kept in control.

Group 2: Rats received a single dose of Streptozoto-cin (STZ) (45 mg/kg/body weight) intraperitonally, the nitrosourea alkylating agent with selective uptake into pancreatic β cells produce diabetes in the rats. The induction of diabetes mellitus was confirmed after 72 h of Streptozotocin treatment by estimation of elevated fasting blood glucose level above ≥250 mg/dl included in this study.

Group 3: STZ induced diabetic rats given pioglitazone drug orally via intragastric (7.5 mg/kg/body weight) for 60 days.

Group 4: STZ induced diabetic rats treated with Zusanli (ST36) acupoint with Acu-TENS stimulator with 15HZ for 60 days.

Electrical stimulation was carried out for 5 min daily at the frequency of 15Hz, pulse width 5 sec, intensity 15mA, using Acu-TENS unit without anesthesia. The positive and negative charges were introduced through electrodes to the right and left Zusanli acupoints, respectively. The experiment was carried out for 60 days, and the blood sample was collected from the tail vein and by retro-orbital venous plexus puncture. Fasting Blood glucose was measured and compared periodically between the groups. β-endorphin and C-peptide levels in the blood serum were measured and compared between the groups.

FIG. 3: Acu-TENS THERAPY AT ZUSANLI ACUPOINTS WITH LOW- FREQUENCY(15HZ), HIGH INTENSITY AND THE PULSE WIDTH OF 5 sec, FOR 5 min DAILY WITHOUT ANESTHESIA FOR 60 DAYS

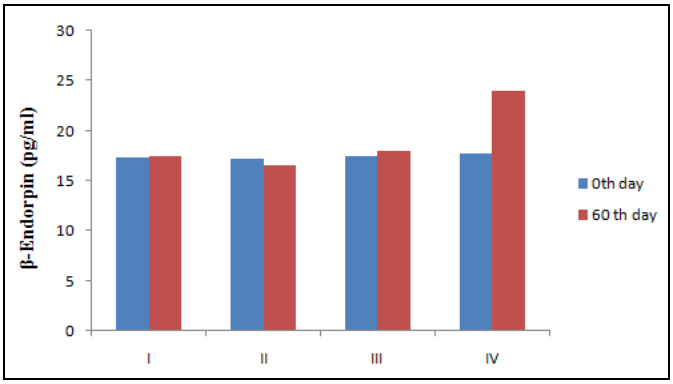
Statistical Analysis: The results were expressed as Mean± SD. The data of blood glucose level, β-endorphin and C-peptide were analyzed by one-way ANOVA followed by Tukey post hoc test for pairwise comparison between the means. The value of p≤ 0.05 was considered as statistically significant.

RESULTS: A significant decrease (p≤0.01) in fasting blood glucose in the toxicity rats was observed at the end of 60th day treatment and was compared to the control and pioglitazone (7.5 mg/kg/bwt) groups showed in **Table 1**. Graph 1 & 2 showed the serum β-endorphin and C- peptide levels were significantly (p≤0.01) increased in the bilateral Zusanli acupoint treated rats and compared with pioglitazone group. Increasing β-endorphin activates the specific receptors in the pancreatic β cells and secrete insulin that results in a decrease in blood glucose levels, considered the mechanism of Acu-TENS therapy at Zusanli acupoints.

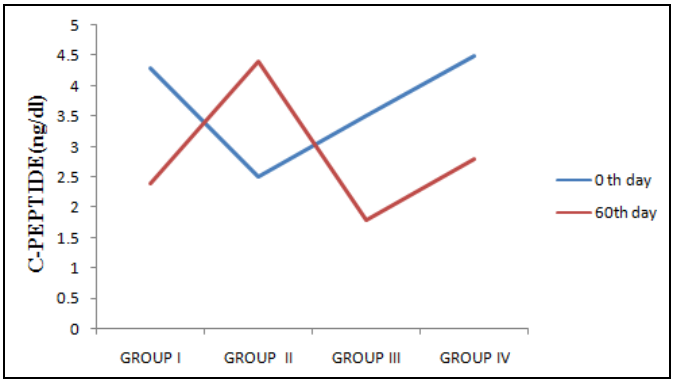
TABLE 1: EFFECTS OF ST36 ON FASTING BLOOD GLUCOSE LEVEL (mg/dl)

Groups	Fasting Blood Glucose Level mg/dl (Mean ±SD)		
	0th day	30th day	60th day
I (control)	91.83 ±24.95	97.67 ±10.11	98.5 ±15.42
II (STZ-induced diabetic,45mg/kg/bwt)	262.33 ±32.34	308.83 ±14.46	369.5 ±27.18
III (pioglitazone, 7.5mg/kg/bwt)	318.5 ±37.37	98.83 ±12.83	72.67 ±10.54
IV (Zusanli acupoint with 15Hz)	293 ±81.09	244 ±57.42	141.33 ±21.97

The results were expressed as Mean ± SD. A comparison was done between control and diabetic groups with one way ANOVA and Tukey test with (p≤0.01).



GRAPH 1: EFFECTS OF ZUSANLI (ST36) ACUPOINT ON β-ENDORPIN (pg/dl). The results were expressed as mean ± SD. A comparison was done between the control and diabetic group with one-way ANOVA and Tukey test with (p≤0.01).



GRAPH 2: EFFECTS OF ZUSANLI (ST36) ACUPOINT ON C-PEPTIDE (ng/dl). The results were expressed as mean ± SD. Comparison was done between control and diabetic groups with one way ANOVA and Tukey test with (p≤0.01).

DISCUSSION: Streptozotocin, a compound of glucosamine-nitrosourea, is toxic to pancreatic beta cells and induces diabetes in experimental animals. Diabetes is one of the major public health problems worldwide. For patient everyday medication and insulin was economically high compared to acupuncture treatment. Now a day peoples showing interest in alternative therapies, mainly acupuncture, due to low therapeutic costs. Recently acupuncture therapy has spread throughout the World. Increasing evidence from scientific research is demonstrating the effectiveness of electro-acupuncture for treating various diseases and revealing the mechanism of action. From a biochemical analysis, acupuncture is believed to stimulate the nervous system, influencing the productions of the body's communication substances like hormones and neurotransmitters. The process of homeostasis activating the body's self regulating systems, thus stimulating its natural healing abilities and promoting physical and emotional well being [25].

In this study, we found that Acu-TENS therapy at bilateral Zusanli acupoints resulted in a significant reduction in fasting blood glucose levels with an increase in β-endorphin and C-peptide levels in the toxicity induced diabetic rats. Hui - Ching Pai *et al*., study shows EA (15HZ) at bilateral Zusanli (ST36) acupoint stimulation with rosiglitazone proves hypoglycemic effect due to an increase in insulin secretion and through the mediation of β-endorphin in normal and STZ-induced type 2 diabetic rats [22]. In this study, we stimulated Zusanli acupoint with Acu-TENS unit and found a significant reduction of fasting blood glucose with an increase in serum β- endorphin and compared with the standard drug (pioglitazone) group. Shih-Liang Chang *et al*., explained EA(2HZ) stimulation at both Zusanli acupoints (ST36) resulted in a hypoglycemic effect with an increase in plasma β-endorphin and insulin in STZ induced diabetic rats[26].In this study, we selected Acu-TENS (15HZ) to stimulate Zusanli acupoint and found the hypoglycemic effect with an increase in serum β-endorphin and C-peptide levels. Dr. Mehmet and Cho Sha *et al*., explained electro-acupuncture has a significant influence in lower blood glucose levels of type 2 DM, lowering cholesterol level, decreasing free-fatty acid, eliminating diabetic neuropathy, and lowering body mass index [27, 28].

In our previous study, we noted that Acu-TENS therapy at Zusanli acupoint restored the body weight, food, and water intake in induced diabetic rats. Fengxia Liang *et al*., explained the hypoglycemic effect with low frequency (3HZ) electro-acupuncture stimulation at ST36/Zusanli acupoint in type 2 diabetic mice [29]. In this study, we found that the hypoglycemic effect of Acu-TENS Zusanli acupoint in diabetic rats. Yu-Chen Lee *et al.* explained electro-acupuncture at the ST36 acupoint produces a hypoglycemic effect due to stimulation of a cholinergic nerve in STZ-induced diabetic rats [10].

In our study, the Acu-TENS stimulation at Zusanli acupoint reduces the blood glucose level may be due to selective stimulation of muscle contraction in STZ induced diabetic rats. According to Chung-Yuh Tzeng *et al.,* explained intracellular signaling pathways associated with glucose- lowering effect of ST36 electro-acupuncture in STZ-induced diabetic rats[30]. P. V. Ingle *et al*., stated the decrease in fasting blood glucose and lower level of TC, TG, LDL, and increase HDL with stimulation of ST36 acupoint with Accu-stimulator apparatus in type 2 diabetes [31]. In our study, using the Accu-Stimulator apparatus shows the reduction of fasting blood glucose with an increase in β-endorphin and C-peptide levels.

According to traditional Chinese medicine, acupuncture therapy can be practiced either manual or electrical with Acu needles. Zhi-Qi-Zhao *et al*., mentioned that in electro-acupuncture, the stimulating current is delivered to acupoints via the acu needles connected to an electrical stimulator. Instead of the insertion of acupuncture needles, a surface electrode on the skin over the acupoints is also described as electro-acupuncture [32].

Hence, in our study, we selected the Acu-TENS apparatus to stimulate the Zusanli acupoint with pen-type electrodes in rats, which results in a hypoglycemic effect. Wu Zhiyuan *et al*., explained the effect of TENS at specific acupoints (LI11, LI4, ST36, SP6) on type 2 diabetes patients for 30 minutes for each session and 5 times a week for 2 months. In our study, stimulation of a single Zusanli acupoint for 5 minutes daily for 60-day treatment in diabetic rats shows a significant decrease in fasting blood glucose (FBG) level.

Acu-TENS, non-invasive technique, has the beneficial effect of preventing the risk of infection, especially to diabetic patients [33]. Some previous research shows that the transcutaneous electrical muscle stimulation with a low stimulation frequency could be an effective method to enhance glucose metabolism [34, 35]. We selected Acu-TENS stimulator due to its combined effect of both electrical and acupoints stimulation. Wu Zhiyuan *et al*., explained treatment with Acu-TENS (10 HZ for 30 minutes) at several acupoints in type 2 diabetes patients produced a beneficial effect on blood glucose level [33]. Catalogna *et al*., explained utilization of glucose and improved hepatic insulin sensitivity in rats with peripheral electrical stimulation (PES) treatment with 2-3 min [37].

In this study, Acu-TENS with the frequency of 15 HZ (low frequency) produced a positive effect in reducing blood glucose level in type 2 diabetes with increase β-endorphin. Hence, the result of the present study suggests that non-invasive acupuncture therapy is a beneficial and cost-effective treatment for elderly type 2 diabetes mellitus patient.

CONCLUSION: We concluded that Acu-TENS therapy at Zusanli (ST36) acupoints produced its hypoglycemic effect might due to the role of β-endorphin. The other advantages of Acu-TENS therapy with low frequency and high-intensity electrical stimulation at bilateral ST36 acupoint causes muscle contraction and mild muscular twitching, which was similar to that of the physiological process of physical exercise. Hence, this therapy can be useful for elderly diabetes patients who were not able to perform physical exercise. We suggest Acu-TENS therapy a cost-effective non-invasive alternative therapy for diabetic patients not only to control diabetes but also to prevent its complications.

ACKNOWLEDGEMENT: Nil

FINANCIAL SUPPORT AND SPONSORSHIP: Nil

CONFLICTS OF INTEREST: There are no conflicts of interest.

REFERENCES:

1. Goud BJ, Dwarakanath V and Swamy BKC: Streptozotocin – A diabetogenic agent in animal models. International Journal of Pharmacy and Pharmaceutical Research 2015; 3(1): 253-69.
2. Subbulakshmi, Sivakumar G and Murthy SSN: Effect of Acu-TENS therapy on Zhongwan (CV12) acupoint in Streptozotocin induced diabetes rats. International Journal of Pharma and Bio Science 2017; 8(3): 1053-58.
3. Akter a S, Rahman MM, Abe SK and Sultana P: Bulletin of the World Health Organisation 2014; 92: 204-213A.
4. Kaveeshwar SA and Wall JC: Australation Medical Journal "Update 2014" IDF International Diabetes Federation (IDF) 2014; 7(1): 45-48.
5. Joshi SR and Parikh RM: India – diabetes capital of the World: 2007: Now heading towards hypertension: J Assoc physicians India 2007; 55: 323-4.
6. Kumar A, Goel MK, Jain RB, Khannap and Chandhary V: India towards diabetes control: key issues. Australas Med J 2013; 6(10): 524-31.
7. Joshi SR and Parikh RM: India – diabetes capital of the World: Now heading towards hypertension. J Assoc physicians India 2007; 55: 323-4.
8. Rizzos CV, Elisat MS, Mikhailidis DP and Liberopoulos EN: How safe is the use of thiazolidinediones in clinical practice? Expert Opinion on Drug Safety 2009; 8(1): 15-32.
9. Hamnvik OPR and McMohan GT: Balancing risk and benefit with oral hypoglycemic drugs. Mt Sinai J of Med 2009; 76(3): 234-43.
10. Lee YC: Electroacupuncture at the Zusanli (ST36) acupoint induces a hypoglycemic effect by stimulating the cholinergic nerve in a rat model of streptozotocine-induced insulin-dependent diabetes mellitus. Evid Based Complementary Alternat Med 2010; 2011(1-6).
11. Ashby TD and Frier BM: Circulating c-peptide measurement and clinical application. Annals Clin Biochem 1981; 18: 125.
12. Ferranini E and Cobelli C: The kinetics of insulin in man. Role of the liver. Diabetes Metab Rev 1987; 3: 365-97.
13. Chailurkit L: Insulin and C-Peptide Levels, Pancreatic Beta Cell Function, and Insulin Resistance Across Glucose Tolerance Status in Thais. Journal of Clinical Laboratory Analysis 2007; 21: 85-90.
14. Ishizaki N, Okushi, Yano NT and Yamamura Y: Improvement in glucose tolerance as a result of enhanced insulin sensitivity during electro-acupuncture in spontaneously diabetic Goto-Kakizakirats. Metabolism 2009; 58(10): 1372-78.
15. Chang SL, Lin JG, Chi TC, Liu IM and Cheng JT: An insulin-dependent hypoglycaemia induced by electro-acupuncture at Zhongwan (CV12) acupoint in diabetic rats. Diabetologia 1999; 42(2): 250-55.
16. Shapira MY, Appeibaum EY, Hirshberg B, Mizrahi Y, Bar-On H and Ziv E: A sustained, non-insulin related, hypoglycaemic effect of electro-acupuncture in diabetic Psammomys obesus. Diabetologia 2000; 43(6): 809-13.
17. Chen KW, Liu T, Zhang H and Lin Z: An analytical review of the Chinese literature on Qigong therapy for diabetes mellitus. Am J of Chin Med 2009; 37(3): 439-57.
18. Nakamura H, Ishigami T, Kawase Y, Yamada A, Minagawa M, Fukuta H, Kurono Y and Suzuki H: Effects of acupuncture stimulation on blood glucose concentration in the Otsuka Long Evans Tokushima fatty(OLETF) rat, an animal model for type-2 diabetes mellitus. Med Sci Monit Basic Res 2014; 20: 70-75.
19. Lin RT, Tzeng CY, Lee YC, Chen YI, Hsu TH, Lin JG and Chang SL: Acupoint-specific, frequency-dependent and improved insulin sensitivity hypoglycemic effect of Electro-acupuncture applied to drug combined therapy

studied by a Randomised control clinical trial. Evid Based Complementary Alternat Med 2014; 1-9.
20. Peplow PV and Baxter GD: Electroacupuncture for control of blood glucose in diabetes: Literature review. J Acupunct Meridian stud 2012; 5(1): 1-10.
21. Figueiredo LM, Silva AH and do prado Neto AX: Electroacupuncture stimulation using different frequencies (10 and 100 Hz) changes the energy metabolism in induced hyperglycemic rats. Acta Cir Bras 2015; 26: 47-52.
22. Pai HC, Tzeng CY, Lee YC, Chang CH, Lin JG, Cheng JT and Chang SL: Increase in plasma glucose lowering action of Rosiglitazone by Electroacupuncture at bilateral Zusanli Acupoint (ST36) in rats. J Acupunct Meridian Stud 2009; 2(2): 147-51.
23. Goldstein A and Lowery PJ: Effect of the opiate anatagonist naloxone on body temperature in rats. Life Science 1975; 17(6): 927-31.
24. Reid RL: Beta-endorphin stimulates the secretion of insulin and glucagon in diabetes mellitus. Metabolism 1984; 33(3): 197-9.
25. www.acupuncture.org.uk. British Acupuncture Council, Nov 2014, 1-5.
26. Chang SL, Tsai CC and Lin JG: Involvement of serotonin in the hypoglycemic response to 2HZ electro-acupuncture of Zusanli acupoint (ST36) in rats. Neuroscience letters 2005; 379(1): 69-73.
27. Cabioglu MT and Ergene N: Changes in levels of serum Insulin, C-Peptide and glucose after Electroacupuncture and Diet Therapy in obese Women. Am J Chin Med 2006; 34(3): 367-76.
28. Cho SH: Acupuncture for obesity: a systematic review and meta-analysis. Int J Obes 2009; 33: 183-196.
29. Liang F, Chen R, Nakagawa A, Nishizawa M, Tsuda S, Wang H and Koya D: Low-frequency electro-acupuncture improves insulin sensitivity in obese diabetic mice through activation of SIRT1/PGC-1α in skeletal muscle. Evid Based Complementary Alternat Med 2010; 2011: 1-9.
30. Tzen CYg, Lee YC, Ho TY, Chen YI, Hsu TH, Lin JG, Lee KR and Chang SL: Intracellular signaling pathways associated with the glucose- lowering effect of ST36 electro-acupuncture in streptozotocin-induced diabetic rats. Acupunct Med 2015; 0: 1-5.
31. Ingle PV, Samdani NR, Patil PH, Pardeshi MS and Surana SJ: Application of acupuncture therapy in type 2 diabetes mellitus patients. Int J Pharma Sci 2011; 2(1): 18-26.
32. Zhao ZQ: Neural mechanism underlying acupuncture analgesia .Progress in Neurobiology 2008; 85: 355-75.
Wu Zhiyuan W, Ming Y, Jie J, Yi W, Tiansheng H, Mingfen L, Zhijie H, Zhenzhen G and Pang LMC: Effect of transcutaneous electrical nerve stimulation at acupoints on patients with type 2 DM: a randomised controlled trial. J Tradit Chin Med 2015; 35(2):134-140.
33. Xu S, Wang L, Cooper E, Zhang M, Manheimer E, Berman B, Shen X and Lao L: Adverse events of acupuncture: a systematic review of case reports. Evid Based Complementary Alternat Med 2013; 1-15.
34. Greenway F and Zheng J: Electrical stimulation as treatment for obesity and diabetes. J Diabetes Sci Technol 2007; 1(2): 251-59.
35. Hamada T, Hayashi T, Kimura T, Nakao K and Moritani T: Electrical stimulation of human lower extremities enhances energy consumption, carbohydrate oxidation, and whole body glucose uptake. J Appl Physiol 2004; 96(3): 911-16.
36. Catalogna M, Fishman S, Halpern Z, Ben-Shlomo S, Nevo U and Ben-Jacob E: Regulation of glucose dynamics by non-invasive peripheral electrical stimulation in normal and insulin-resistant rats. Metabolism 2016; 65(6): 863-73.

How to cite this article:
Subbulakshmi R and Sivakumar G: The role of β- endorphin and c-peptide in streptozotocin induced diabetic rats with effect of Acu-TENS at Zusanli (ST36) acupoints. Int J Pharm Sci & Res 2020; 11(12): 6532-38. doi: 10.13040/IJPSR.0975-8232.11(12).6532-38.