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A Study on the Role of K Channels in Regulation of Vascular Reactivity in Diabetic Rats

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Abstract

Background: Diabetes Mellitus (DM) is a major international health problem characterized by an absolute or relative deficiency in the production or action of insulin, which results in hyperglycemia. Unfortunately, long term insulin administration in patients with DM results in insulin resistance. In this work, a novel therapeutic strategy of one of the ATP sensitive K channel opener KATP openers called Nicorandil was tried as an adjuvant agent in ameliorating CVD in experimentally-induced type I DM in rats.

Aim of Study: The present study was designed to elucidate possible role of K channels in glucose homeostasis and regulation of the vascular reactivity in diabetic rats.

Material and Methods: Fifty adult male albino rats were used in this investigation, divided into following groups control: Non-diabetic (C), diabetic (D), diabetic insulin treated (D + I), diabetic nicorandil treated (D + N) and diabetic insulin and nicorandil treated (D + I + N). Blood samples were collected for estimation of Fasting Blood Glucose (FBG) and (HbA_{1c}), and vascular reactivity was examined using different vasoactive agents.

Results: Type 1 DM resulted in substantial alterations in biochemical variables, as fasting blood glucose level, HbA_{1c}, ABP and vascular reactivity.

In our study there is significant decrease in fasting blood glucose level, (HbA_{1c}) in both diabetic insulin (D + I) treated group and diabetic insulin and nicorandil (D + I + N) treated group in compared with the diabetic group, but with insignificant change between the two groups. There was significant improvement in vascular reactivity in diabetic insulin (D + I) treated group, diabetic nicorandil (D + N) treated group and diabetic insulin and nicorandil (D + I + N) treated group in compared with the diabetic (D) non treated group, but with insignificant change between insulin and nicorandil (D + I + N) treated group and non-diabetic (C) group.

Conclusion: Nicorandil can be used as an adjuvant therapy in diabetic rats to improve vascular reactivity.

Key Words: *Nicorandil – K channels – Vascular reactivity – Rats.*

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Introduction

DM is a chronic metabolic disorder that represents a serious public health concern. It is characterized by defective insulin secretion and or inappropriate insulin hormone action. Untreated DM is usually associated with a wide range of cardiovascular complications **[1,2]**.

Vascular diseases are the principal causes of death and disability in people with diabetes. The macrovascular manifestations include atherosclerosis and medial calcification. The microvascular consequences including retinopathy and nephropathy are major causes of blindness and end-stage renal failure **[3]**.

Diabetes contributes to defects in the autonomic nervous system, the endothelium, and local metabolism, all of which can result in microvascular disease. Diabetic Autonomic Neuropathy (DAN) is one factor associated with impaired autoregulation of blood flow in a variety of vascular beds, including the skin and the heart **[4]**.

Diabetic vasculopathy with dysfunction of ion channels particularity KATP has been also implicated due to oxidative stress **[5,6]**.

Nicorandil, an ATP-dependent potassium (KATP) channel opener, has been introduced as a nitric oxide donor, an antioxidant and antianginal drug **[7,8]**. Also, it was proved to improve the diabetic state and the ameliorated rat islet β-cell damage induced by streptozotocin in vivo and in vitro **[9]**. So, it has been assigned for the management of vascular issues with DM.

The aim of this work is to spot a beam of light on the possible role of K channel in glucose homeostasis and regulation of the vascular reactivity in diabetic rats.

Material and Methods

The present study was carried out at Physiology Department, Faculty of Medicine, Menoufia University, Egypt at February 2019.

Experimental animals:

Fifty adult male albino rat of local strain, weighing (200-250) grams each were used in this work. Rats were got from a licensed trainer, kept on standard laboratory chow, water & libitum, housed in the animal house in cages measured 70 X 70 X 60cm, 5 animals/cage under normal light/dark cycle.

Study design:

Throughout the study period, the animals were classified into the following groups.

- *Group I:* Control non diabetic (n=10) (C) group: Rats were injected subcutaneously with saline in a dose of 0.2ml/100gm B.W/day, 6 days per week for 8 weeks.
- *Group II:* Diabetic non treated (n=10) (D) group: Diabetes mellitus was induced by a single intraperitoneal injection of STZ (60mg/Kg) in 10 mmol/L in citrate buffer (pH 4.5) **[10]**.
- *Group III:* Diabetic insulin treated (n=10) (D + I) group: Diabetic rats were treated with mixtard insulin subcutaneously in a dose of 0.75IU/100 gm B.W, once daily, 6 days per week for 8 weeks **[11]**.
- *Group IV:* Diabetic (nicorandil) treated (n=10) (D + N) group: Diabetic rats were administered daily for 8 weeks. Nicorandil was provided as tablets (20mg/tablet), they were grinded, dissolved in D.W and administered to the rats via oral gavage tube at a dosage of (15mg/kg) **[12]**.
- *Group V:* Diabetic insulin and nicorandil treated (10 rats) (D + I + N) group: Diabetic rats were treated with combined insulin and nicorandil. Mixtard insulin was injected subcutaneously in a dose of 0.75IU/100gm B.W 6 days per week and nicorandil via oral gavage at a dose (15mg/kg) for 8 weeks.

Chemicals: Streptozotocin, (STZ) (Sigma Chemical Company, USA), kits for estimation of serum glucose (Biodiagnostic Company, Egypt), kits for estimation of glycosylated hemoglobin (Riomidi, France), A-II (Sigma-Aldrich Chemical Co. Steinheim, Germany), Noradrenaline NE (Alex. Co. For Egypharma, Egypt), SNP (El-Gomhoria Company, Egypt), Ach. (El-Gomhoria Company, Egypt).

Blood samples and biochemical assay:

At the end of the experimental period (8 weeks), 1-Rats were fasted for 12 hours, morning retro-orbital venous blood samples were collected using fine heparinized capillary tubes for measuring HbA_{1_c}. Other blood samples were collected in a clean graduated centrifugal tube, were left for clotting for 30 minutes at room temperature and then centrifuged at 3000rpm for 15 minutes. Serum samples were collected for estimation of fasting blood glucose. Then the rats were anesthetized by thiopental sodium and the femoral artery is identified and cannulated using a cannula pre-filled with heparinized normal saline. The other end of the cannula was connected to pressure transducer. The invasive blood pressure was recorded using physiography system and vascular reactivity to various vasoactive drugs was recorded.

Statistical analysis:

The IBM Company - SPSS program (Chicago, USA, SPSS Inc.) version 16.0 was used for analysis of data. The results were expressed as mean ± SD. The significance of differences between groups was determined by one-way analysis of variance with the post hoc of Tukey's multiple comparison tests. *p*-values <0.05 were considered statistically significant.

Results

The presented Fig. (1) demonstrates the fasting blood glucose level of the different experimental groups.

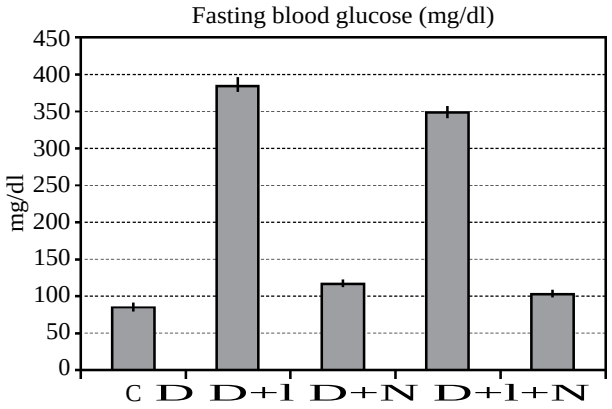

Fig. (1): Fasting serum glucose level (mg/dl) in control (C), diabetic non treated (D), diabetic insulin treated (D + I), diabetic nicorandil treated (D + N) and diabetic insulin and nicorandil treated (D + I + N) groups.

On measurement of (FBG), in diabetic (D) group, it was significantly higher (p<0.05) when compared to (C), (D + I) and (D + I + N) treated groups and insignificantly changed when compared to (D + N) treated group. In diabetic insulin (D +

I) treated group, it was significantly higher when compared to (C) group, significantly lower (p<0.05) when compared to (D + N) treated group and insignificantly changed when compared to (D + I + N) treated group. In diabetic insulin and nicorandil (D + I + N) treated group, FBG was significantly lower when compared to (D + N) treated group and significantly higher when compared to (C) group.

The presented Fig. (2) demonstrates the HbA_{1c} level of the different experimental groups.

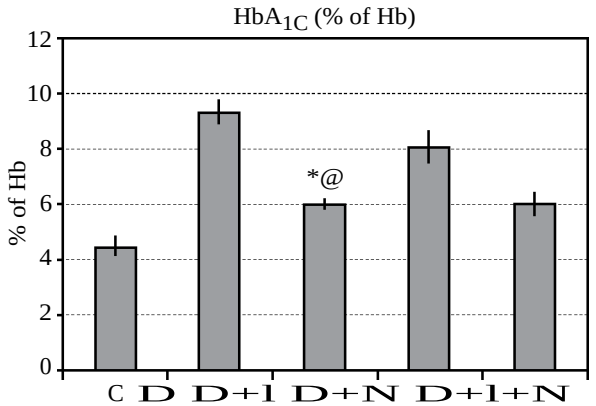

Fig. (2): Level of (HbA_{1c}) as a percentage of normal Hb in control (C), diabetic non treated (D), diabetic insulin treated (D + I), diabetic nicorandil treated (D + N) and diabetic insulin and nicorandil treated (D + I + N) groups.

On measurement of (HbA_{1c}), in diabetic (D) group, (HbA_{1c}) as percentage of normal Hb was significantly higher (p<0.05) when compared to (C), (D + I) and (D + I + N) treated groups and insignificantly changed when compared to (D + N) treated group. In diabetic insulin treated (D + I) group, it was significantly higher when compared to (C) group, significantly lower (p<0.05) when compared to (D + N) treated group and insignificantly changed when compared to (D + I + N) treated group. In diabetic insulin and nicorandil (D + I + N) treated group, (HbA_{1c}) level % was significantly lower when compared to (D + N) treated group and significantly higher when compared to (C) group.

The presented Fig. (3) demonstrates the basal Mean Arterial Blood Pressure level (MABP) of the different experimental groups.

The MABP in diabetic (D) group was significantly higher (p<0.05) compared to all other groups. In diabetic insulin (D + I) treated group, it was significantly higher (p<0.05), when compared to the corresponding values of (C) group and significantly lower (p<0.05), when compared to (D + N) and (D + I + N) treated groups. In diabetic insulin and nicorandil (D + I + N) treated group, it was significantly lower (p<0.05), when compared to the corresponding values of (D + N) treated group and insignificantly changed (p>0.05), when compared to the corresponding values of (C) group.

The presented Fig. (4) demonstrates the Heart Rate (HR) of the different experimental groups.

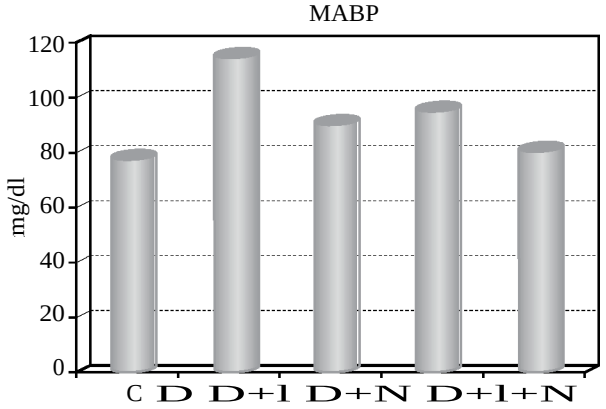

Fig. (3): The basal mean arterial blood pressure of the different experimental groups, control (C), diabetic non treated (D), diabetic insulin treated (D + I), diabetic nicorandil treated (D + N) and diabetic insulin and nicorandil treated (D + I + N) groups.

Fig. (4): Demonstrates the basal heart rate of the different experimental groups, control (C), diabetic non treated (D), diabetic insulin treated (D + I), diabetic nicorandil treated (D + N) and diabetic insulin and nicorandil treated (D + I + N) groups.

The heart rate in diabetic (D) group was significantly lower (p<0.05) compared to all other groups. In diabetic insulin (D + I) treated group, it was significantly lower (p<0.05), when compared to the corresponding values of (C) group and significantly higher (p<0.05), when compared to (D + N) and (D + I + N) treated groups. In diabetic insulin and nicorandil (D + I + N) treated group, it was significantly higher (p<0.05), when compared to the corresponding values of (D + N) treated group and insignificantly changed (p>0.05), when compared to the corresponding values of (C) group.

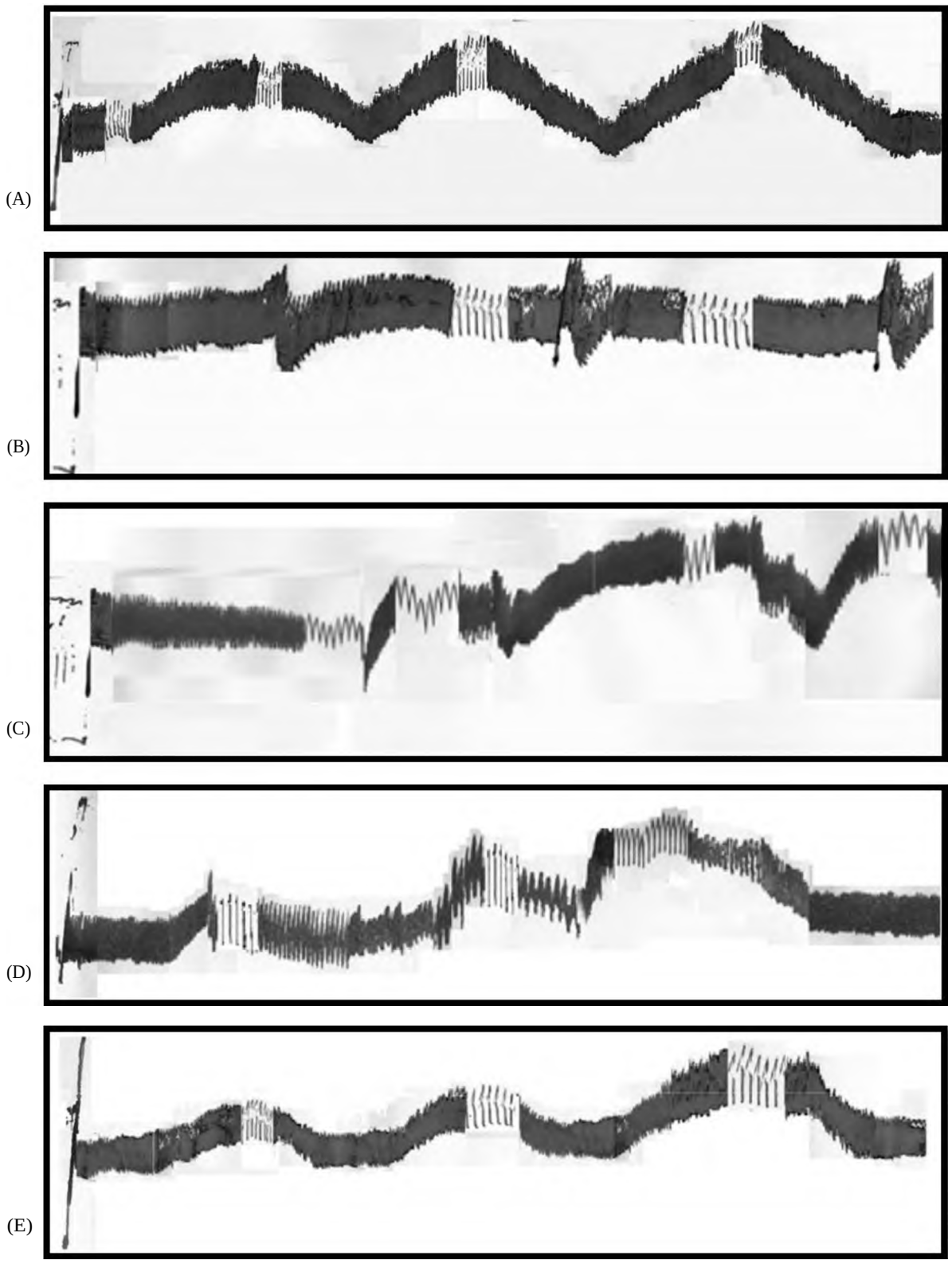

Fig. (5): Demonstrates the effect of different doses of A-II (20, 40 and 60) ng on vascular reactivity of femoral artery.

In diabetic non treated (D) group of A-II induced a rise of basal MABP and a decrease of basal HR which were found significantly lower ($p<0.05$) when compared to the corresponding values of all other groups.

In diabetic insulin treated (D + I) group, A-II induced a rise of basal and decrease of basal HR which were found significantly higher ($p<0.05$) when compared to the corresponding values of (D + N), significantly lower ($p<0.05$) when compared

to the corresponding values of (C) and (D + I + N) groups.

In diabetic insulin and nicorandil treated (D + I + N) group, A-II induced a rise of basal MABP and decrease of basal HR which were found significantly higher ($p<0.05$) when compared to the corresponding values of (D + I) and (D + N) trea-ted groups and insignificantly changer ($p>0.05$) when compared to the corresponding values of (C) group.

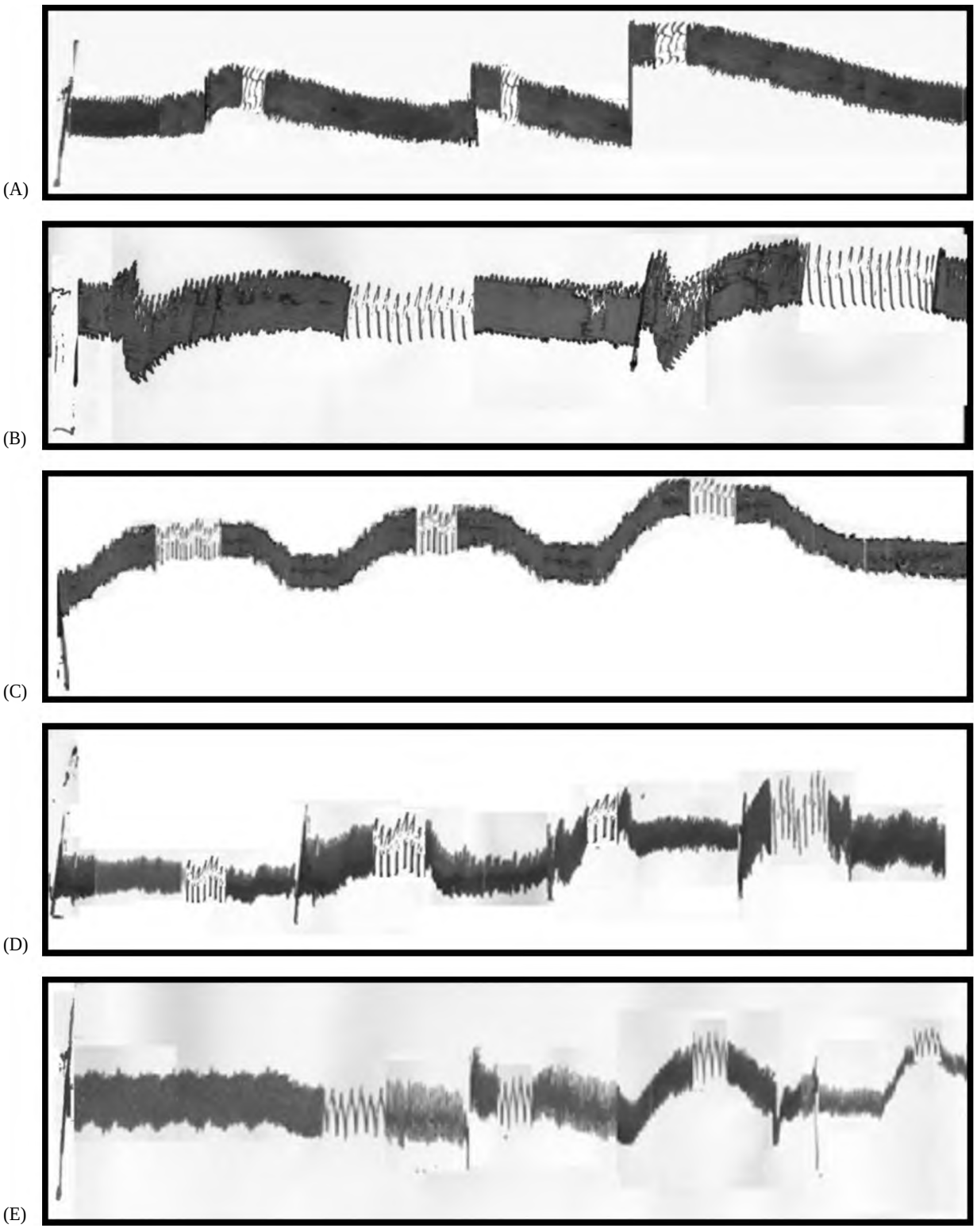

Fig. (6): Demonstrates the effect of different doses of NE in doses of 100, 200 and 400ng on vascular reactivity of femoral artery.

In diabetic non treated (D) group of NE induced a rise of basal MABP and a decrease of basal HR which were found significantly lower ($p<0.05$) when compared to the corresponding values of all other groups.

In diabetic insulin treated (D + I) group, NE induced a rise of basal and decrease of basal HR which were found significantly higher ($p<0.05$) when compared to the corresponding values of (D + N), significantly lower ($p<0.05$) when compared to the corresponding values of (C) and (D + I + N) groups.

In diabetic insulin and nicorandil treated (D + I + N) group, NE induced a rise of basal MABP and decrease of basal HR which were found significantly higher ($p<0.05$) when compared to the corresponding values of (D + I) and (D + N) treated groups and insignificantly changer ($p>0.05$) when compared to the corresponding values of (C) group.

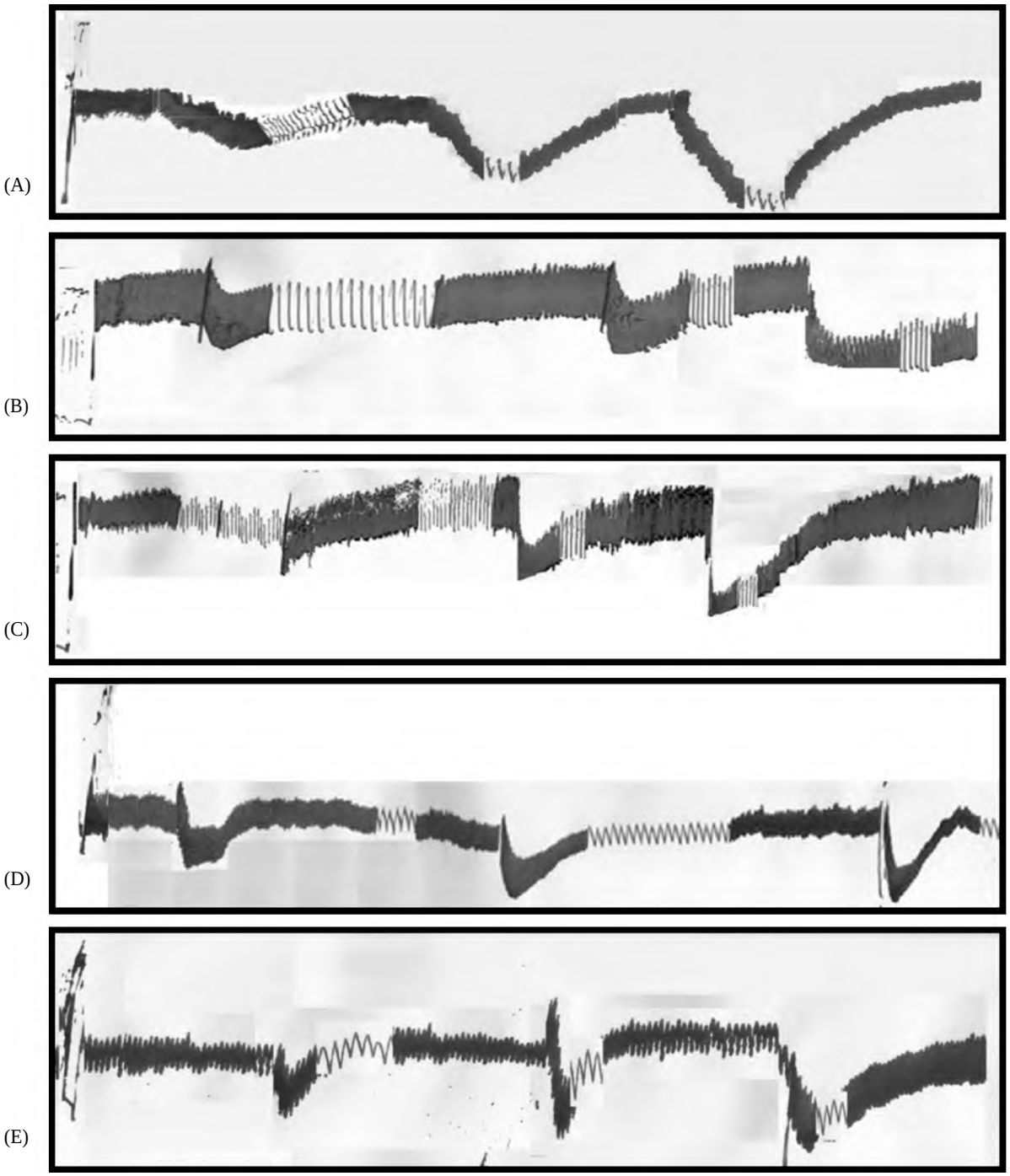

Fig. (7): Demonstrates the effect of different doses of (Ach) 1 X 10^{-9}, 1 X 10^{-8} and 1 X 10^{-7} M on vascular reactivity of femoral artery.

In diabetic non treated (D) group, (Ach) induced a decrease of basal MABP and decrease of basal HR, which were found significantly lower (p<0.05), when compared to the corresponding values of all groups.

In diabetic insulin treated (D + I) group, (Ach) induced a decrease of basal MABP and decrease of basal HR, which were found significantly lower (p<0.05) when compared to the corresponding values of (C) and (D + I + N) groups, significantly higher (p<0.05), when compared to the corresponding values of (D) group and insignificantly changed (p>0.05), when compared to the corresponding values of (D + N) treated group.

In diabetic insulin and nicorandil treated (D + I+ N) group, (Ach) induced a decrease of basal MABP and decrease of basal HR, which were found significantly higher (p<0.05) when compared to the corresponding values of (D + N) treated group, and insignificantly changed (p>0.05) when compared to the corresponding values of (C) group.

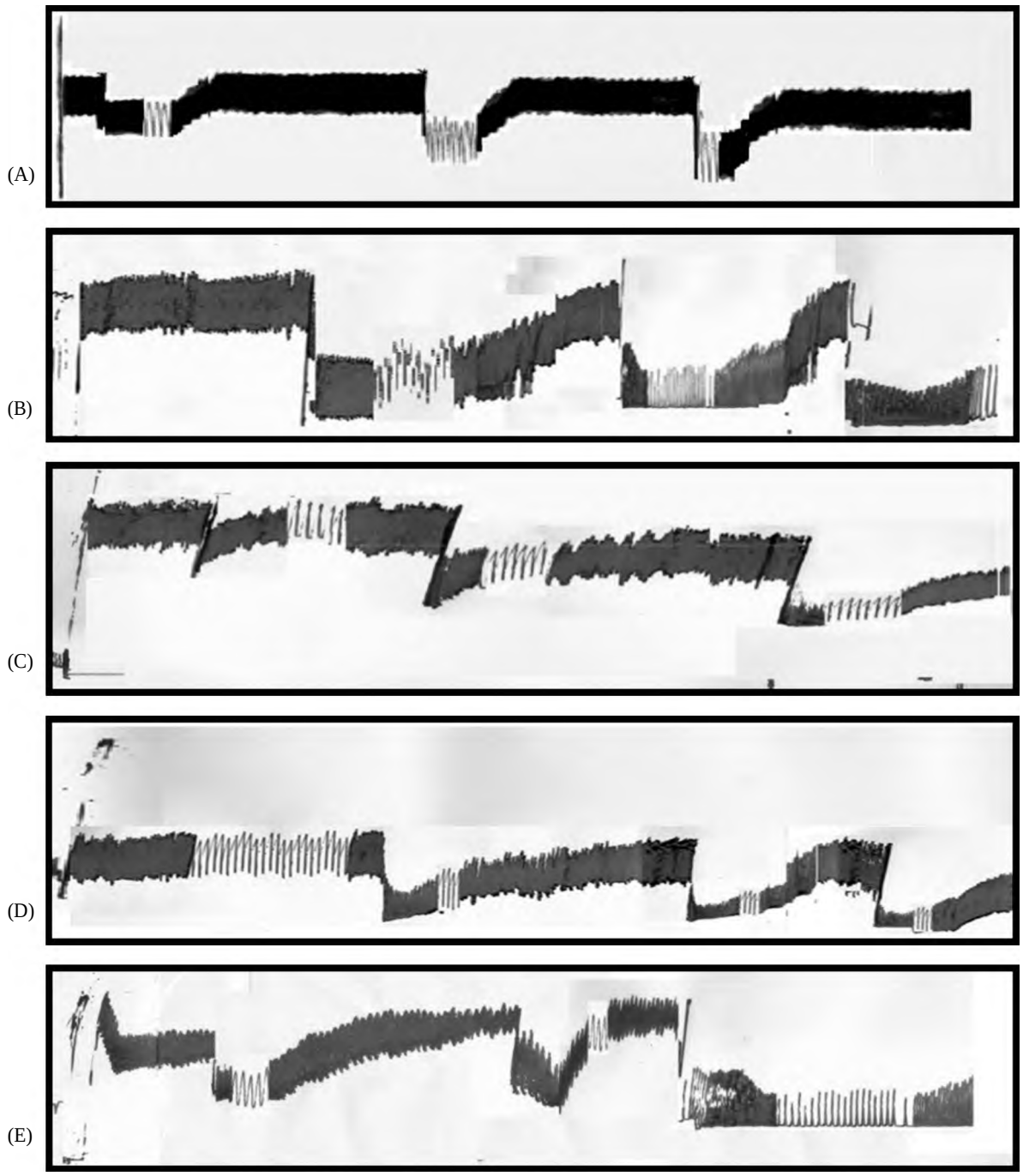

Fig. (8): Demonstrates the effect of different doses of (SNP) 1, 2 and 4µg on vascular reactivity of femoral artery.

In diabetic non treated (D) group, (SNP) induced a decrease of basal MABP and increase of basal HR, which were found significantly lower (p<0.05), when compared to the corresponding values of all groups.

In diabetic insulin treated (D + I) group, (SNP) induced a decrease of basal MABP and increase of basal HR, which were found significantly lower (p<0.05) when compared to the corresponding values of (C) and (D + I + N) groups, significantly higher (p<0.05), when compared to the corresponding values of (D) group and insignificantly changed (p>0.05), when compared to the corresponding values of (D + N) treated group.

In diabetic insulin and nicorandil treated (D + I+ N) group, (SNP) induced a decrease of basal MABP and increase of basal HR, which were found significantly higher (p<0.05) when compared to the corresponding values of (D + N) treated group, and insignificantly changed (p>0.05) when compared to the corresponding values of (C) group.

Discussion

Diabetic vascular changes cannot be corrected by insulin only and depends on the start of treatment and its duration. So, application of Nicorandil can promote more vascular improvement in diabetic blood vessels.

In the present study, following injection of STZ there was a significant increase in the serum glucose concentrations compared to the corresponding values in the non-diabetic group. These results were in line with the reports of many researchers that stated that, following STZ injection in animals, almost β-cells undergo necrosis with consequent insulin deficiency and an overwhelming hyperglycemia **[13]**. In this work, insulin administration for 8 weeks to the diabetic rats (in insulin treated group) could significantly change the serum insulin and the glucose levels compared to these obtained results of the diabetic group. In support with these findings, Stang & Story **[14]**, had found that insulin is the most effective medication that lowers blood glucose levels in diabetes. Insulin serves as the primary regulator of blood glucose by increasing glucose uptake in muscle and fat tissues. It stimulates the translocation of the glucose transporter GLUT4. There was significant elevation in glucose level in both diabetic and diabetic/nicorandil-treated groups compared to the control group. Highly significant elevation of glucose levels in the diabetic group mainly due to diabetic action of STZ **[15]**. This result was in agreement with Kunjathoor et al., **[16]** who concluded that plasma glucose levels in mice treated with STZ nearly doubled and may be maintained for at least 16 weeks. The marked reduction in pancreatic islets number contributes to the decreased plasma insulin levels and hyperglycemia observed in STZ-treated mice. But as observed in the diabetic/nicorandil-treated group still glucose level significantly higher than control group, however relative to diabetic group non-significant difference still existed, this mean that treatment with nicorandil did not improve glycemic state and this result in agreement with Mano et al., **[17]**, who demonstrated that 15mg/kg/day nicorandil has no effect on plasma glucose in STZ-induced diabetic rats, but this finding was against Kasono et al. **[18]**, who demonstrated that nicorandil improved diabetes in rat beta cell damage induced by STZ in vivo and in vitro probably by a free radical scavenging effect. In this study, HbA_{1_c}% in the diabetic group was significantly higher than that of the non-diabetic group. These results coincided with Nakhaee et al., **[19]**, who had found that HbA_{1_c}% increases in STZ-induced diabetic rats and the rate of its increase was directly proportional to the hyperglycemic state. Clinically, HbA_{1_c}% measurement reflects control of the mean blood glucose level over 2-3 months period in cases of DM. Therefore, follow of diabetic patients by measurement of HbA_{1_c}% is considered a definitive sensitive index of long term control of diabetes and its consecutive decline is associated with reducing diabetic complications **[20]**. Insulin treatment for 8 weeks to the diabetic rats resulted in a significant decrease in HbA_{1_c}% when compared to the corresponding values in diabetic group. In support with these findings Bhatia & Aggarwa **[21]**, found that HbA_{1_c}% improves with administration of proper dose insulin in diabetic subject which indicates glycemic control over the last 3 months.

In the present study, regarding to the arterial blood pressure and heart rate, the diabetic non treated rats showed a significant increase of mean ABP with reciprocal decrease of heart rate, when compared to the control rats. These results were in agreement with Mota et al., **[22]**, who stated that this developed hypertension is due to the endothelial dysfunction which can be considered an early marker of cardiovascular diseases and contributes partially to increase arterial blood pressure levels. Ozçelikay et al. **[23]** concluded that increase arterial blood pressure might be due to increase production of lipid peroxides as MDA. These results were in disagreement with several other studies such as Montero et al. **[24]**, who reported that unchanged arterial blood pressures could be observed in some diabetic subjects and Wu et al. **[25]**, who found that autonomic cardiovascular reflexes altered by hy-

perglycemia leads to hypotension and it may be associated with cardiomyopathy induced by its metabolic disturbance.

Insulin treatment to diabetic rats for 8 week induced a significant decrease in the mean ABP with reciprocal increase of heart rate when compared to the diabetic non treated group. These results were in agreement with Monfredi et al., **[26]**, who found that improvement of HR and ABP after insulin treatment might be due to its ability to repair autonomic dysfunction induced by hyperglycemia. Aulbach et al. **[27]** and Hyltén et al. **[28]** reported that increasing heart rate by insulin treatment in diabetic rats is due to stimulation of the L-type Ca2+ current in SAN cells.

Results of this study revealed a significant decrease in the mean ABP with reciprocal increase in the heart rate in rats treated with nicorandil therapy when compared to the diabetic non treated rats. This hypotensive effect of Nicorandil is mostly due to its KATP sensitive channel opener activity and its vasodilator property, it up-regulates eNOS and results agreed with inhibits the ROS-induced uncoupling of this enzyme and subsequently increases the endothelial NO production that causes dilatation of the blood vessels **[29]**. In addition, it is reported that Nicorandil improved vascular endothelial dysfunction in STZ-induced rats through its anti-oxidant property.

In addition, the present results revealed that combined nicorandil and insulin treatment for 8 week to diabetic rats was able to restore of mean ABP and heart rate to normal level seen in the control group. These results indicate the beneficial effect of concomitant use of nicorandil with insulin to decrease ABP in diabetic rats.

Regarding vascular reactivity of femoral artery measurement, the diabetic non treated group showed a significant decrease of vascular reactivity to all doses of vasopressors (A-II and NE) and vasodilators (Ach and SNP), when compared to the control group. These results were in agreement with several other studies such as Baluchnejadmojarad et al., **[30]** and Saleh et al., **[31]**, who explained such vascular impairment by non-enzymatic protein glycation, sorbitol myoinositol changes and generation of ROS. Rajendran et al. **[32]**, stated that chronic hyperglycemia in cases of DM is associated with an increase in oxidative stress which causes endothelium damage due to increased production of ROS and the damaged endothelium cannot produce vasodilators such as NO.

Regarding the diabetic insulin treated rats, there was a significant increase of vascular reactivity to all doses of vasopressors (AII and NE) and vasodilators (Ach and SNP), when compared to the diabetic non treated rats. These results were in agreement with Kobayashi and Kamata **[33]**, who postulated that insulin administration increases sensitivity of blood vessels to vasoconstrictors such as catecholamines by stimulating alpha adrenergic receptors in rat vascular smooth muscle cells.

In the present, nicorandil administration for 8 weeks induced a significant increase of vascular reactivity to all doses of vasodilators (Ach and SNP) when compared to the diabetic non treated group. In line with these findings Eguchi et al., **[34]** proved that nicorandil opens KATP channels in vascular smooth muscle increases trans membrane potassium conductance hyperpolarization of the smooth muscle cells relaxation of vascular wall decrease blood pressure.

Conclusion:

Nicorandil can be used as an adjuvant therapy in diabetic rats.

Treatment of diabetic rats by combined insulin and nicorandil for 8 weeks is able to restore vascular reactivity to vasopressors and vasodilators near to the normal level. In support with these findings, Gao et al., **[35]** had found that diabetic vascular changes cannot be corrected by insulin only and depends on start of treatment and its duration. So, application of alternative method or/and drugs can promote more vascular improvement in diabetics blood such as nicorandil which increases the sensitivity to insulin.

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دراسة تأثير ممرات البوتاسيوم على تنظيم تفاعلية الأوعية الدموية فى الجرذان المحدث بهم مرض البول السكرى تجريبياً

خلفية البحث: مرض البول السكرى هو مشكلة صحية دولية رئيسية تتميز بنقص مطلق أو نسبى فى إنتاج أو عمل الأنسولين، مما يؤدى إلى إرتفاع السكر فى الدم. لسوء الحظ، يؤدى إعطاء الأنسولين على المدى الطويل إلى مقاومة الأنسولين. وعدم علاج مرض البول السكرى يعرض المريض لعدة أضرار بسبب زيادة نسبة الجلوكوز فى الدم من أخطرها أنه يؤدى إلى خلل وظائف القلب والأوعية الدموية بسبب الإجهاد التأكسدى والذى يؤدى إلى تغيير فى جدار الأوعية الدموية وخلل فى وظيفة البوابات المتحكمة فى حركة الأيونات الموجودة فى جدار الأوعية الدموية والتى من أهمها ممرات البوتاسيوم. وفى هذا البحث تم إستخدام عقار النيكورانديل الفاتح لبوابات البوتاسيوم والمضاد للأكسدة ومعطى لأكسيد النيتريك كما أنه يقلل من الأضرار الواقعه على خلايا لانجرهانز.

الهدف من البحث: تأثير عقار النيكورانديل الفاتح لبوابات البوتاسيوم على توازن الجلوكوز وتفاعليه الأوعية الدموية فى الفئران المصابة بمرض البول السكرى.

مواد وطرق البحث: تم تقسيم ٥٠ من ذكور الفئران البيضاء البالغه إلى ٥ مجموعات الأولى ١٠ فئران كمجموعة ضابطة والثانية ١٠ فئران تعرضوا للإصابة بمرض البول السكرى والثالثة ١٠ فئران تم علاجهم بالأنسولين والرابعة ١٠ فئران تم علاجهم بعقار النيكورانديل والخامسة ١٠ فئران تم علاجهم بالأنسولين والنيكورانديل.

النتائج: إستخدام النيكورانديل أدى إلى تحسن ملحوظ على تفاعلية الأوعية الدموية للأنجيوتنسين والنورادرينالين والأستيل كولين والصوديوم نيتروبروسيد وضغط الدم الشريانى لكنه لم يؤثر على مستوى السكر فى الدم ولذا فمن الممكن إستخدامه كوسيلة مساعده مع الأنسولين فى علاج النوع الأول البول السكرى.