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A study on the effect of adropin on blood pressure in male albino rats

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ABSTRACT

Adropin is a peptide hormone involved in insulin sensitivity and cardiac function. The relationship of adropin and vascular functions is still in controversy, no available data demonstrated the effect of adropin on blood pressure. *Objective*: Demonstrating the effect of adropin on blood pressure in normal and induced hypertensive rats. 48 male albino rats were divided into 6 groups: Control (C), Adropin treated (AT), Uninephrectomized (UNX), UNX-adropin treated (UNX+A), DOCA salt hypertensive (DOCA) and DOCA salt-adropin treated (DOCA+A). Adropin reduced significantly systolic and diastolic pressures in both UNX+A group in comparison with UNX one (P≤ 0.0001) and in DOCA+A group (P≤ 0.0001) in comparison with DOCA group. Diastolic pressure was decreased

significantly in adropin treated group (P≤ 0.05) in comparison with control group. *Conclusion*: According to available resources, this study is the first investigating the direct effect of adropin on blood pressure. Adropin decreased significantly diastolic pressure in both normal and induced hypertensive rats but reduced significantly systolic pressure only in hypertensive rats. Adropin might be a therapeutic agent in treatment of hypertension however, further studies on human are recommended.

Keywords: adropin, blood pressure, vascular, hypertensive, DOCA.

1. INTRODUCTION

Hypertension is a chronic disease affecting nearly one billion people all over the world and is responsible for high morbidity and mortality rates (Yu et al., 2014). Hypertension in 90 - 95% of cases is idiopathic and in 5 - 10% of cases, hypertension is secondary to renal, endocrine, or other diseases. Incidence of hypertension in obese individuals is 1.7 - 3.4 times greater than lean individuals (Sayin et al., 2014; Carretero & Oparil., 2000). Hypertension represents one of the major outstanding dangerous causes of counteractive cardiovascular CV) problems (Kannel, 1996). Increased blood pressure is mostly due to impairment in the endothelial function and vascular hazards (Panza et al., 1996). 24-hour blood pressure observation is helpful in the diagnosis of hypertension and estimation of BP control and variance. The definition of HT is based on the averaged 24-h systolic BP more than 130 mmHg or diastolic BP more than 80 mmHg (Bolayir et al., 2018).

Peptides have an essential role in dispatching metabolic state to maintain cardiovascular and metabolic homeostasis. Many studies suggested adropin to be the signal of this metabolic condition (Butler et al., 2018). Adropin was first described to be an output of the Energy Homeostasis Association (ENHO) gene, composed of two-exons on human chromosome which is Adropin$^{1-76}$ (full length) (Kumar et al., 2008). Adropin$^{1-33}$ is the secretory peptide, however, Adropin$^{34-76}$ is biologically active when mice and rats were treated with, causing alteration in glucose and lipid metabolism (Gao et al., 2015; Butler et al., 2019). Adropin$^{34-76}$ may share in maintenance of regulation of endothelial nitric oxide synthase function and activity (Chen et al., 2017). Adropin is illustrated in numerous tissues (e.g. brain, liver, umbilical vein and coronary artery (Chen et al., 2015) and was suggested to have a role in energy equilibrium, control the sensitivity of insulin, and function of the cardiovascular system (Yu et al., 2014).

Sayin et al. (2014) stated that the obesity is connected with reduced concentrations of the circulating adropin. It is described that a reduction in the adropin level with obesity may result in participation in the pathogenicity of dyslipidemia and tolerance of insulin (Kumar et al., 2012). In mice models, obesity either diet-induced or genetically induced is accompanied with reduced appearance of the adropin transcription in liver and reduced adropin levels in blood. The decreased adropin effect in obesity may consequently participate in the progress of insulin resistance and dyslipidemia. In addition, mice with adropin-knock out displays high adiposity, increased triglycerides (TG), increased resistance to insulin, and augmented the tendency for diminished glucose tolerance with diet-induced obesity (Butler et al., 2012; Akcilar et al., 2016).

Limited investigations have been assessed the correlation between cardiovascular diseases and levels of adropin (Lian et al., 2011). Lovren, et al. (2010) demonstrated the vascular effect of adropin and they found that adropin was expressed in the endothelial cells of human, increased nitric oxide (NO) release, and stimulated vascular endothelial growth factor receptor 2. They also reported an endothelial protective effect of adropin via activation of endothelial NO synthase expression. In addition, Topuz et al. (2013) reported that the level of adropin was decreased in patients suffered from endothelial impairment compared to those with normal function. They reported that adropin level was negatively linked to the seriousness of atherosclerosis. Polkowska et al. (2019) confirmed that the levels of the regulatory peptides including adropin were higher in children with coexistent diseases, such as autoimmune thyroid diseases, dyslipidemia and hypertension. The adropin level was diminished in young patients suffering from sleep apnea due to obstructive causes and endothelial impairment in comparison with the control (Gozal et al., 2013). All these studies confirmed the relationship of adropin and vascular functions, therefore, we hypothesized that adropin might have an effect on blood pressure. According to our available resources, the effect of adropin on blood pressure had never been previously investigated; consequently, the current investigation was planned to demonstrate an adropin effect on blood pressure in normotensive and hypertension induced in rats.

2. MATERIALS AND METHODS

Experimental design

A total of 48 male albino rats (150–200 g) were obtained from the faculty of veterinary medicine, Zagazig University, Egypt. Rats were kept in 24 h (light-dark cycle) at approximately 26°C, and had freely water and food access for one week for acclimatization before starting the study.

Ethical Approval

All experiments were accomplished based on the ethical recommendations for the veterinary health care in Zagazig University (Experimental protocol approval No, 447/2019/59).

Drugs and chemicals

Adropin (34-76) (human, mouse, rat) was purchased from NovoPro Bioscience Inc. Company, China. DOCA was bought from (Sigma Aldrich, U.S.A.). Adropin was dispersed in purified water (18) while DOCA was liquefied in Dimethyl Sulfoxide (DMSO) (Prahalathan et al., 2012).

Method of uninephrectomy

A total of 32 rats were used for Left uninephrectomy. Ketamine (75 mg/kg) was injected in all rats after intra-peritoneal anesthesia. One cm long left lateral abdominal incision was carried out to expose kidney. Left renal artery and ureter were ligated with a thread of silk and the left kidney was removed. Muscle and skin were sutured (Prahalathan et al., 2012).

DOCA-salt hypertensive rats

After uninephrectomy, rats were permitted for drinking water without additional medications. In hypertensive groups received DOCA-salt, NaCl (1%) was added to the drinking water, followed by subcutaneous injection of DOCA (25 mg/kg, twice weekly) with mild heating for six consecutive weeks (Iyer et al., 2010).

Experimental protocol

(8 rats/ group)

Control (C) group: given distilled water.

Adropin treated group (ATG): adropin (2.1 µg/kg body weight/day) dissolved in distilled water and injected intraperitoneal once each morning (9-10 a.m.) for 6 weeks (Lovren et al., 2010).

Uninephrectomized group (UNX): given vehicle.

UNX-adropin treated group (UNX+A): the uninephrectomized rats were injected adropin (2.1 µg/kg body weight/day)dissolved in distilled water and injected intraperitoneal once each morning (9-10 a.m.) for 6 weeks (Lovren et al., 2010).

DOCA salt hypertensive group (DOCA): given subcutaneous injections of DOCA (25 mg/kg, twice weekly) for 6 weeks (Iyer et al., 2010).

DOCA salt-adropin treated group (DOCA+A): given subcutaneous injection of DOCA (25 mg/kg, twice weekly) for 6 weeks (Iyer et al., 2010) with injection of adropin intraperitonealy (2.1 µg/kg body weight/day) dissolved in distilled water once each morning (9-10 a.m.) for 6 weeks (Lovren et al., 2010).

Measurement of blood pressure

Blood pressure was measured twice weekly throughout the study period using the tail-cuff technique. Rats were put in chambers for 15 min at approximately 30–34 °C, then 9 blood pressure measurements were registered per each rat. The average of the lower most 3 recordings was taken as a mean (X) blood pressure. Measurements and analysis were carried out using a computerized method (Zhang et al., 2013).

Statistical analysis

SPSS version 21 (SPSS for Windows) was used in our study to analyze the data. The statistical significance of the differences was estimated via unpaired Student's *t*-test. Statistical significance was represented at p value ≤ 0.05.

3. RESULTS

Table 1 & chart 1 showed insignificant differences between the control group and the adropin treated group in systolic blood pressure in all weeks. In 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks, systolic blood pressure in uninephrectomized group was increased significantly (P≤ 0.05, ≤ 0.05, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively), however, in uninephrectomized rats treated with adropin, the systolic pressure was significantly reduced in comparison with UNX group (P= 0.04, = 0.01, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively).

In DOCA group, the systolic pressure was increased significantly in all study period, compared with the UNX group (P≤ 0.0001). DOCA group treated with adropin showed a significant decrease systolic pressure in the 1st day, 2nd, 3rd, 4th, 5th and 6th weeks (P= 0.04, = 0.003, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively) in comparison with DOCA group.

Table 1 Effect of adropin on systolic blood pressure (mmHg)

	C	ATG	UNX	UNX+A	DOCA	DOCA+A
Day1	100±2	98±2	105±4*a (P≤ 0.05)	101±3*b (P= 0.04)	125±4*b (P≤ 0.0001)	120±5*c (P= 0.04)
1st w	110±3	108±2	116±5*a (P≤ 0.05)	110±4*b (P= 0.01)	130±6*b (P≤ 0.0001)	121±4*c (P= 0.003)
2ndw	113±2	111±2	122±3*a (P≤ 0.0001)	114±4*b (P≤ 0.0001)	140±5*b (P≤ 0.0001)	130±3*c (P≤ 0.0001)
3rd w	111±3	110±2	127±3*a (P≤ 0.0001)	115±4*b (P≤ 0.0001)	150±5*b (P≤ 0.0001)	131±7*c (P≤ 0.0001)
4th w	115±2	113±3	132±4*a (P≤ 0.0001)	116±3*b (P≤ 0.0001)	160±7*b (P≤ 0.0001)	133±5*c (P≤ 0.0001)
5th w	113±4	111±3	135±5*a (P≤ 0.0001)	115±5*b (P≤ 0.0001)	170±6*b (P≤ 0.0001)	136±7*c (P≤ 0.0001)
6th w	118±5	114±4	140±5*a (P≤ 0.0001)	118±6*b (P≤ 0.0001)	182±7*b (P≤ 0.0001)	140±5*c (P≤ 0.0001)

C: Control. A: Adropin. UNX: Uninephrectomized. DOCA: Deoxy-corticosterone acetate.
Significance level at p < 0.05.
a= p-value of significance versus control group.
b= p-value of significance versus UNX group.
c= p-value of significance versus DOCA group.

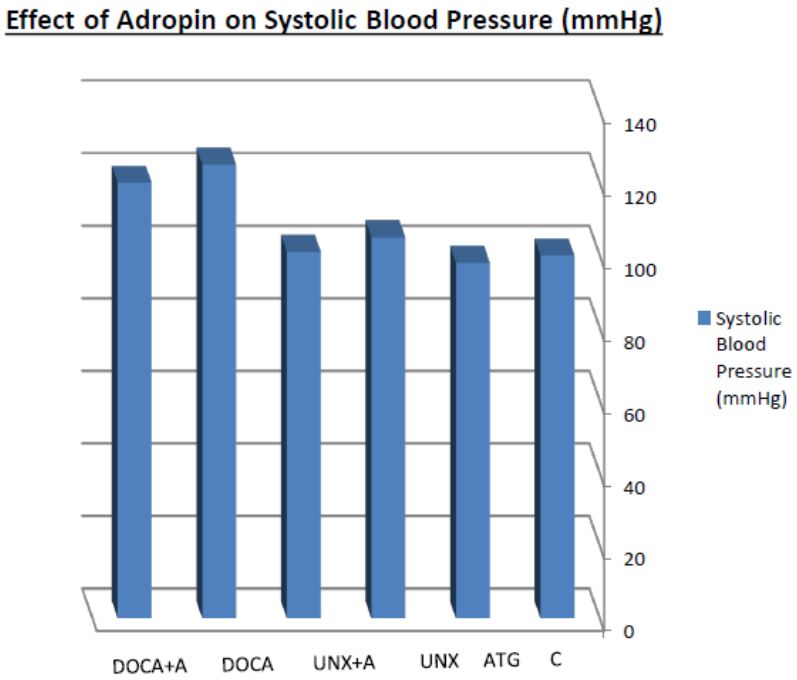

Chart 1 Effect of adropin on systolic blood pressure (mmHg)

Table 2 & chart 2 showed that diastolic pressure was decreased significantly in adropin treated group (C+A) starting from 1st week and afterwards (P≤ 0.05 in 1st, 2nd, 3rd, 4th, 5th and 6th weeks compared with the control group). In the uninephrectomized group diastolic pressure was increased significantly in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks (P≤ 0.0001) compared with the

control group. Adropin decreased significantly diastolic pressure in the UNX+A group compared with the UNX group (P≤ 0.001 1st day, P≤ 0.0001 in 1st, 2nd, 3rd, 4th, 5th and 6th weeks). In the DOCA group diastolic pressure was increased significantly in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks compared with the UNX group (P≤ 0.0001). Adropin produced a significant suppressive effect on diastolic pressure in the DOCA group treated with adropin in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks (P= 0.03, ≤ 0.001, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively) in comparison with the DOCA group.

Table 2 Effect of adropin on diastolic blood pressure (mmHg)

	C	ATG	UNX	UNX+ A	DOCA	DOCA+A
Day1	70±3	70±1	80±1*a (P≤ 0.0001)	77±2*b (P≤ 0.001)	85±3*b (P≤ 0.0001)	82±2*c (P=0.03)
1st w	78±3	75±2*a (P≤ 0.05)	90±3*a (P≤ 0.0001)	83±2***b (P≤ 0.0001)	100±5*b (P≤ 0.0001)	93±4**c (P≤ 0.001)
2ndw	77±3	74±1*a (P≤ 0.05)	91±2*a (P≤ 0.0001)	82±3***b (P≤ 0.0001)	118±5*b (P≤ 0.0001)	108±4***c (P≤ 0.0001)
3rd w	83±2	80±3*a (P≤ 0.05)	94±1*a (P≤ 0.0001)	83±3***b (P≤ 0.0001)	120±4*b (P≤ 0.0001)	107±5***c (P≤ 0.0001)
4th w	81±3	78±1*a (P≤ 0.05)	98±2*a (P≤ 0.0001)	84±3***b (P≤ 0.0001)	125±5*b (P≤ 0.0001)	110±4***c (P≤ 0.0001)
5th w	80±2	77±3*a (P≤ 0.05)	97±3*a (P≤ 0.0001)	81±3***b (P≤ 0.0001)	130±4*b (P≤ 0.0001)	115±3***c (P≤ 0.0001)
6th w	84±4	80±3*a (P≤ 0.05)	99±4*a (P≤ 0.0001)	82±3***b (P≤ 0.0001)	140±5*b (P≤ 0.0001)	110±4***c (P≤ 0.0001)

C: Control. A: Adropin. UNX: Uninephrectomized. DOCA: Deoxy-corticosterone acetate.
Significance level at p < 0.05.
a= p-value of significance versus control group.
b= p-value of significance versus UNX group.
c= p-value of significance versus DOCA group.

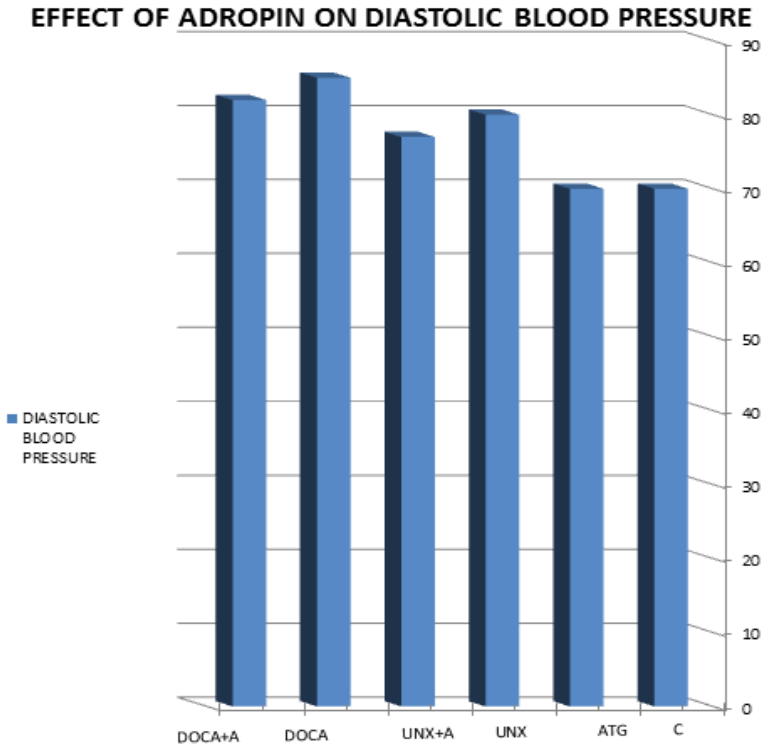

Chart 2 Effect of adropin on diastolic blood pressure (mmHg)

4. DISCUSSION

Adropin is a regulatory peptide maintaining energy homeostasis and reducing food intake and body weight (Kumar et al., 2008). Adropin also plays an essential role in the metabolism of lipid and tolerance of insulin (Kumar et al., 2012). The role of adropin in cardiovascular system was studied by many authors. Lovren et al. (2010) reported a potential capacity of adropin in protecting the endothelium by increased nitric oxide synthase expression. In addition, Lian et al. (2011) demonstrated a significant negative correlation between adropin and left ventricular ejection fraction and they proposed that adropin may contribute in the pathogenicity of heart failure. Moreover, Yu et al. (2014) found that decreased serum adropin level could be a biomarker for expecting the austerity of atherosclerosis (Yu et al., 2014; Wu et al., 2014). All these studies confirmed a relationship between adropin and blood vessels. We postulated that adropin might have a role in regulation of blood pressure, however, no available studies examined its role in blood pressure, so, this study was designated to demonstrate the efficacy of adropin on normotensive as well as hypertensive rats.

In the current research, adropin had the ability to produce an insignificant restrained effect on systolic blood pressure in adropin treated set throughout the study period. In uninephrectomized group, systolic pressure was considerably increased in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks ($P \leq 0.05$, ≤ 0.05, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively). Adropin significantly reduced systolic blood pressure in the uninephrectomized group treated by adropin in comparison with the UNX group in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks ($P = 0.04$, $= 0.01$, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively). There were no significant variations between UNX+A and Control groups which indicates the return of systolic pressure to nearby control values. These results were matched with Chen et al., (2015) who believed that adropin has the ability to regulate blood pressure and they suggested that its exact mechanism maybe as a result of recovering the endothelial impairment, and controlling the action of the nervous system. The present study was also supported by Mattu and Randeva (2013) who showed that blood pressure had been affected by adipokines through controlling of obesity, metabolic processes, and endothelial impairment. However, we are in controversy with Altincik and Sayin (2015) who found that adropin levels are not correlated with BP variables. This controversy may be attributed to species variations where they conducted their investigation on human volunteers as well as the duration of study and size of sample is different where they mentioned that the number of subjects in their study was small.

In this study, systolic pressure was strongly elevated in DOCA treated rats in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks compared with the UNX group ($P \leq 0.0001$). This study found that adropin produced a significant inhibitory effect on systolic pressure in DOCA group treated with adropin in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks ($P = 0.04$, $= 0.003$, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively) in comparison with DOCA group. These results are matched with Stein et al. (2016) who described a central action of adropin inhibiting water intake. They also identified an adropin G protein-coupled receptor, GPR19, in male rats. Reduction of this receptor mRNA levels in hypothalamus resulted in loss of adropin inhibitory effect on thirst resulting from water deprivation.

In the present study, diastolic pressure was decreased significantly in adropin treated group starting from 1st week and afterwards ($Pa \leq 0.05$ in 1st, 2nd, 3rd, 4th, 5th and 6th weeks) compared with control group. In uninephrectomized group diastolic pressure was increased significantly in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks ($P \leq 0.0001$) compared with the control group. Adropin significantly decreased diastolic pressure in UNX+A group compared with the UNX group ($P \leq 0.001$ 1st day, $P \leq 0.0001$ in 1st, 2nd, 3rd, 4th, 5th and 6th weeks). These results are matched with Gu et al. (2015) who found significant lower adropin level in hypertensive patients in comparison with controls and a negative correlation was found between adropin on one hand and diastolic and systolic blood pressure on the other hand. They also found that adropin is negatively correlated with ET-1 (a biomarker for endothelial dysfunction), they considered adropin as a predictor of hypertension. They concluded that the decreased adropin level is associated with hypertension and adropin is a predictor for hypertension, and may affect blood pressure through protecting endothelial function. Also, our findings are enforced by Gulen et al. (2016) who established that adropin increased significantly in normotensive patients in comparison with hypertensive ones.

In DOCA group diastolic pressure was increased significantly in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks compared with the UNX group ($P \leq 0.0001$). Adropin significantly decreased diastolic pressure in DOCA group treated with adropin in 1st day, 1st, 2nd, 3rd, 4th, 5th and 6th weeks ($P = 0.03$, ≤ 0.001, ≤ 0.0001, ≤ 0.0001, ≤ 0.0001 and ≤ 0.0001 respectively) in comparison with DOCA group. These results are matched with Wang et al. (2017) who found a significant increase in adropin levels of preeclamptic women in comparison with normal pregnancy. They suggested that this increase in adropin level may be a compensatory mechanism for preeclampsia.

5. CONCLUSION

According to available resources, this is the first study demonstrating the direct effect of adropin on blood pressure. Adropin significantly reduced diastolic blood pressure in both normotensive and induced hypertensive rats and significantly decreased systolic pressure in hypertensive rats only. Adropin will be a promising therapy in treatment of hypertension; however, indication of adropin in treatment of hypertension needs further studies on human.

Author contributions

First author; created the idea and synthesized the hypothesis then collected the data about this hypothesis. Experimental protocol was also created by the corresponding author. Also, the corresponding author with the second author performed experiments. The two authors shared the writing of results. Corresponding author wrote the discussion then the second author revised it carefully and updated some references. The second author performed editing revision and plagiarism.

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