OPEN ACCESS Pharmacologia

ISSN 2044-4648
DOI: 10.5567/pharmacologia.2016.211.216

Research Article
Antihypertensive Effect of Valoneic Acid Dilactone on Fludrocortisone Induced Hypertensive Rats

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Abstract

Objective: This study evaluated the possible protective effect of valenoic acid dilactone on fludrocortisones induced hypertension in Wister rats. **Methodology:** Fludrocortisones induced reabsorption of salt and water leading to increase in blood volume and hence, increase blood pressure. There is also increased secretion of vasopressin in addition, altered activity of renninangiotensin-aldosterone system (RAAS) leading to increase in sympathatic activity. Valoneic acid dilactone at dose 400 mg kg^{-1} day^{-1} p.o. for 3 weeks was evaluated for its effect on blood pressure and heart rate using non-invasive blood pressure measuring apparatus. Vascular reactivity experiments were performed in segments of aorta from normotensive rats, hypertensive control rats and hypertensive rats treated with valoneic acid dilactine. **Results:** Treatment with valoneic acid dilactone significantly reduced the blood pressure of fludrocortisones salt-treated hypertensive rats. Valoneic acid dilactone administered to normotensive rats for 3 weeks did not alter the mean blood pressure and heart rate. The vascular reactivity to noradrenaline (8.47×10^{-7} to 1.73×10^{-4}) in isolated aortic strip was increased in fludrocortisone salt-treated hypertensive rats. The contractile responses to noradrenalin in isolated aortic strip from hypertensive rats treated with valoneic acid dilactone were significantly reduced than that in the controls. **Conclusion:** The present *in vivo* and *in vitro* studies have shown, that there is increase in vascular reactivity to adrenaline in fludrocortisones salt-treated hypertensive rats. The reduction in vascular reactivity by valoneic acid dilactone suggests that there is alteration in the sensitivity of the adrenoceptor to noradrenalin and adrenaline. Valoneic acid dilactone shows antihypertensive activity in fludrocortisone salt-treated hypertensive rats.

Key words: Valoneic acid dilactone, mineralocorticoid, blood pressure, tail cuff, aortic strip

Received: December 20, 2015 Accepted: March 05, 2016 Published: April 15, 2016

Citation: Mohamed Fouad Shalaby and Alsayed Ahmed Zaki, 2016. Antihypertensive effect of valoneic acid dilactone on fludrocortisone induced hypertensive rats. Pharmacologia, 7: 211-216.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Essential hypertension is mainly related to chronic increase of peripheral vascular resistance and renal reabsorption of sodium and water[1]. It is also well known that most of this increased vascular resistance resulting mainly from functional (changes in vascular reactivity) and/or structural (increased arteriolar wall-to-lumen ratio) abnormalities[2]. Antihypertensive drugs should be able to prevent any of previous changes, which considered during chronic hypertension[3]. The central sympathetic nervous system plays a major role in control of vascular resistance. It was mentioned that proin ammatory cytokines affect vascular function and endothelium-derived factors involved in hypertension[4,5]. These cytokines enhance the formation of a number of endothelial cell substances, such as endothelin, reduce acetylcholine-induced vasodilatation and destabilize the mRNA of endothelial nitric oxide synthase[6-8]. Thus, endothelial dysfunction associated with many forms of hypertension may, in part, be mediated by proin ammatory cytokines. Also supporting a potential role for cytokines in the regulation of arterial pressure are ndings that plasma levels of proin ammatory cytokines correlate with increased blood pressure in certain forms of human hypertension and experimental animal models of hypertension[9-11]. Oxidative stress can affect vascular reactivity by different mechanisms. Reactive oxygen species function as second messengers, activating numerous signalling molecules and play an important role in vascular physiopathology[12,5]. Angiotensin II increases the production of reactive oxygen species, including hydrogen peroxide and nitric oxide that participate in the process of in ammation and elevation of the blood pressure[13-15]. In the present study, the animal model of hypertension share many features, which are common to human hypertension. Different models of hypertension have been developed by excessive salt intake, corticosteroids with strong mineralocorticoid effects, such as fludrocortisone and hyperactivity of rennin angiotensin-aldosterone system (RAAS)[16]. Since regulation of Blood Pressure (BP) is multifactorial, the effectiveness of an antihypertensive agent in one model does not necessarily mean, that the mechanism of action of a given agent in a given model is related to the pathogenesis of elevated blood pressure. Fludrocortisones induced reabsorption of salt and water leading to increase in blood volume and hence increase blood pressure. There is also increased secretion of vasopressin in addition, altered activity of RAAS leading to increase in sympathetic activity[17]. The present study was designed to investigate the possible antihypertensive activity and vascular reactivity alteration by using valoneic acid dilactone in hypertensive rat's model.

MATERIALS AND METHODS

Animals: Male albino Wistar rats 100-150 g were used. The study was conducted according to the National Institutes of Health guidelines for the care and use of laboratory animals. All animal care and experimental procedures were carried out with the ethics approval of the local regulatory authority. The animals were kept at ventilated cages with controlled temperature with a 12/12 h dark/light cycle, which allowed us to perform experiments in the active phase of the animals. Rats were habituated to laboratory conditions. Rats received a standard diet and water.

Drugs and chemicals: Valoneic acid dilactone was purchased from Triveni Interchem Private Limited, India. Noradrenalin and Fludrocortisone acetate were purchased by Sigma-Aldrich, USA. All other chemicals used in the study were of analytical grade. The valoneic acid dilactone was dissolved in deionized water and administered orally.

Mineralocorticoid induced hypertension: Groups of rats were kept on a diet high in sodium chloride and drinking water was replaced by 2% sodium chloride solution. After they attain a weight of about 250 g, they were given fludrocortisones dissolved in sesame oil at dose of 10 mg kg^{-1} once daily for 3 weeks[18].

Hypotensive activity in normotensive rats: Normotensive rats of either sex were randomly assigned into 3 groups (n = 3). Group 1 represented normal control, group 2 and 3 received 200 and 400 mg kg^{-1} p.o. of valoneic acid dilactone, respectively. Basal blood pressure and heart rates were measured at 0, 2, 4 and 6 h using non-invasive blood pressure recorder apparatus (Ugo basile instruments, Varese, Italy). Each rat was placed in restrainer and appropriate cuff with sensor was mounted on its tail and warmed to about 33-35°C. The tail cuff was inflated to a pressure above 200 mmHg, systolic blood pressure, diastolic blood pressure and heart rate were measured directly by the tail cuff and pulse sensor[19].

Antihypertensive activity in hypertensive rats: Three groups (n = 3) of hypertensive rats (250±10 g) were treated orally once daily with deionized water, 10 mL kg^{-1} (control), valoneic acid dilactone 200 and 400 mg kg^{-1} for three weeks. The systolic blood pressure and heart rate were measured by non-invasive blood pressure recorder apparatus before and after treatment. The rats were initially trained for blood pressure measurement on at least three separate occasions to establish a baseline blood pressure.

Vascular reactivity experiments: Vascular reactivity was studied in aortic segments by isometric tension[20]. Two parallel stainless steel pins were introduced through the lumen of the segments: One was fixed to the organ bath wall and the other one was connected to a force transducer (Ugo basile, Italy), which in turn was connected to an amplifier. Segments were incubated in an organ bath containing 25 mL of Krebs-Henseleit solution at 37±0.5°C, continuously bubbled with a 95% O_2-5% CO_2 mixture (pH 7.4). An optimal resting tension of 1.5 g was applied to all aortic segments[21,22]. This tension was adjusted every 15 min during a 60 min equilibration period before adding drugs. The vessel rings were equilibrated for 1 h with the tension of 2.0 g and pre-contracted with KCl (60 mM) to produce the maximal KCL-induced contractile plateau. Subsequently the cumulative dose–response curve for noradrenaline (NA) (10^{-10} to 10^{-5} M) was obtained. The values of the NA-induced contraction were expressed as a percentage of maximal contraction induced by KCl. The dose response curve of nor-adrenalin (8.47×10^{-7} to 1.73×10^{-4}) was studied on the isolated aortic strips of hypertensive rats and hypertensive rats treated with VAD.

Data analysis and statistics: Results are expressed as Mean±SEM of the number of rats indicated, differences were analyzed using student's t-test. The $p<0.05$ was considered as statistically significant. The Vasoconstrictor responses induced by noradrenalin were expressed as a percentage of the tone generated by 75 mM KCl. Straight lines (log dose response curves) was drawn by linear regression.

RESULTS

Hypotensive activity in normotensive rats: In normotensive rats, all the used VAD at doses 200 and 400 mg kg^{-1} did not show any appreciable hypotension effect and did not affect HR on normotensive rats compared to baseline values (Table 1 and 2).

Antihypertensive activity: Oral administration of fludrocortisones once daily caused significant rise in blood pressure after 3 weeks of administration. Daily oral administration of the different doses of VAD caused a variable decrease in blood pressure. The VAD at a dose of 200 and 400 mg kg^{-1} produced a significant ($p>0.05$) antihypertensive effect after three weeks of treatments (Table 3). The VAD at dose 200 mg kg^{-1} demonstrated a remarkable decrease in heart rate at week 2 and 3. The VAD at dose 400 mg kg^{-1} demonstrated a significant ($p>0.05$) decrease in heart rate of hypertensive rats at the end of week 3, compared to hypertensive control group (Table 4).

Contractile response of vascular ring to NA: Vascular dysfunction is related to increased vasoconstriction and weakened diastolic function. Therefore, It is important to determine whether there is any change in the vascular function by detecting the vascular reactivity of aortic rings to a physiological modulator, noradrenalin (NA). Cumulatively

Table 1: Effect of valoneic acid dilactone on the systolic blood pressure of normotensive rats

	Normotensive rats (SBP mmHg±SEM)	
	Treatments	
Time (h)	200 (mg kg^{-1})	400 (mg kg^{-1})
0	118±1.08	123±1.02
2	115±1.10	115±1.18
4	121±0.99	117±0.77
6	112±0.87	122±0.81

SBP: Systolic blood pressure, all values are mean of 5 observations±SE

Table 2: Effect of valoneic acid dilactone on the heart rate of normotensive rats

	Normotensive rats (Heart beats per minute±SEM)	
	Treatments	
Time (h)	200 (mg kg^{-1})	400 (mg kg^{-1})
0	385±2.99	372±3.22
2	371±3.01	420±3.84
4	451±3.21	397±3.44
6	402±3.88	375±3.72

All values are mean of 5 observations±SE

Table 3: Effect of valoneic acid dilactone on systolic BP of hypertensive rats on continuous therapy for 21 days

	Hypertensive rats (SBP±SEM)			
	Days			
Treatment	0	7	14	21
Normal control	110.50±3.64	110.83±3.38	90.50±0.81	112.30±1.89
Hypertensive control	145.16±0.79*	144.83±1.47*	155.40±1.41*	140.11±1.63*
PGE 200 (mg kg^{-1})	143.50±1.31	152.40±1.89	131.20±0.89**	123.90±1.29**
PGE 400 (mg kg^{-1})	146.10±1.38	143.20±0.83	128.40±1.12**	119.26±0.89**

SBP: Systolic blood pressure, all values are mean of 5 observations ±SE, *$p<0.05$ compared to normal control group, **$p<0.05$ compared to hypertensive control group

Table 4:Effect of valoneic acid dilactone on heart rate of hypertensive rats on continuous therapy for 21 days

	Hypertensive rats (Heart beats per minute±SEM)			
	Days			
Treatment	0	7	14	21
Normal control	411.33±3.64	387.30±3.45	378.7±3.64	418.14±3.89
Hypertensive control	445.16±2.79	444.73±4.47*	455.10±4.41*	440.11±3.63
PGE 200 (mg g^{-1})	443.50±3.31	452.30±3.89	431.20±3.89	423.90±3.29
PGE 400 (mg kg^{-1})	446.40±3.38	443.40±3.83	435.40±1.12	376.25±2.89**

*p<0.05 compared to normal control group, **p<0.05 compared to hypertensive control group, all values are mean of 5 observations±SE

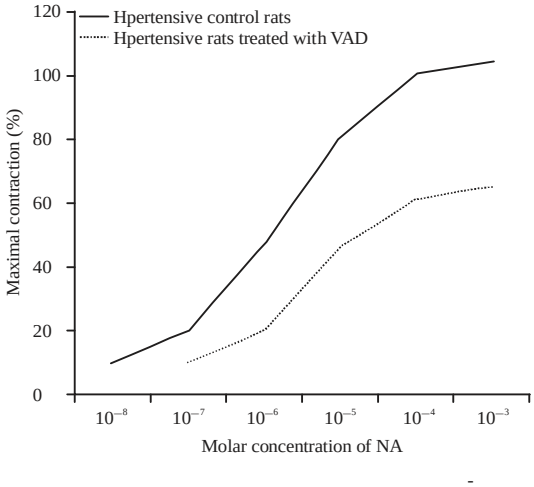

Fig. 1: Cumulative dose-response curve to noradrenaline in aortic strips of rats made hypertensive by DOCA (hypertensive control rats) and hypertensive rats treated with valoneic acid dilactone (400 mg kg^{-1}). p<0.05 compared to hypertensive control group

added NA (10^{-10} to 10^{-5} M) caused concentration-dependent contractile responses in isolated aortic rings. Hypertensive control group significantly increased the vasoconstrictive response to NA (p<0.01), VAD treatment decreased the vasoconstrictive effect than that of fludrocortisones treated group (p<0.01) (Fig. 1). Furthermore, the contractile responsiveness to NA of the VAD treated group was significantly lower than that of the control group (p<0.01) (Fig. 1). Treatment with VAD (400 mg kg^{-1} day^{-1} p.o. for 3 weeks) in the DOCA salt-treated rats significantly (p<0.001) shifted the dose-response curve of noradrenalin to the right in isolated aortic strip as compared to the dose-response curve of the hypertensive control animals.

DISCUSSION

In the present study, the hypertension induced by fludrocortisones in rats may be due to the retention of sodium and water followed by increase in the blood volume[23]. It has been further shown that the altered membrane permeability in the fludrocortisones-salt-treated hypertensive models causes abnormal cation turnover[24]. This abnormal cation turnover leads to vasoconstriction and finally to increased arterial blood pressure. The increased vascular sensitivity to noradrenalin in fludrocortisones-salt-treated hypertensive rats is also due to increased mobilization of calcium ion into the vascular smooth muscle[25]. It is possible that the alterations in voltage operative calcium channels or calcium permeability are the main reasons for the maintenance of hypertension in the fludrocortisones-salt-treated hypertensive model[26,27].

Valoneic acid dilactone is a derivative of hydroxybenzoic acid. The present study shows that VAD has a significant antihypertensive effect in experimentally induced hypertensive models. This result agrees with a previous reports[28,29]. The present *in vitro* studies have shown that there is increased vascular reactivity to adrenaline in fludrocortisones-salt-treated hypertensive models. Vasomotion may be associated with changes in K (+) uptake. The previous studies, measured the effect of phenylephrine (PE) and acetylcholine (ACh) on the vascular reactivity in rat aortic rings. The incubation of aortic rings with 10^{-7} M PE and 10^{-6} M ACh produced the highest rhythmic contractions. Both 10^{-7} M PE and 10^{-6} M ACh significantly increased K (+) uptake in endothelium-intact aorta versus control (121% PE and 117% ACh)[30]. The reduction in vascular reactivity by VAD in fludrocortisones-salt-treated hypertensive rats suggests that there is alteration in the sensitivity of the adrenoceptor to adrenaline. These results are in agreed with a previous report[29].

CONCLUSION

Based on the mechanism of hypertension in the fludrocortisones-salt-treated hypertensive models, it is suggested that the antihypertensive effects of VAD might be due to its alteration in the transport of cations across the cell membrane.

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