Persistency of dexamethasone induced hypertension in male wistar rat model

Rat hypertension

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Abstract

Aim: Dexamethasone (Dexa) attenuate the progression of many diseases, but despite its beneficial effects can be caused hypertension (HTN). Material and Method: According to this finding, we study the persistence of Dexa induced HTN. Experimental design includes 30 Adult male Wistar rats that divided into three groups (Dexa2, Dexa3, Control; N=10). Results: Dexa (20µg/kg/day, in a volume of 1 mL/kg) daily was injected subcutaneously for two months (Dexa2) and three months (Dexa3). Systolic blood pressure was measured periodically using the tail-cuff method with a photoelectric sensor (NIPREM 546, Cibertec S.A, Madrid, Spain) along the study. Discussion: We found that 3-month injection of Dexa induced HTN furthermore in rats, persist for two months after withdrawing of injection whereas injection for 2month has less persistency (10days).

Keywords

Dexamethasone; Hypertension; Blood Pressure; Heart Rate

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Introduction

One of the most common cardiovascular diseases is hypertension (HTN) [1] and cause main Concern for societies because of its morbidity and mortality [2]. The prevalence of HTN is significantly different around the world. A research study estimated that the prevalence of HTN in adult and elderly population of Iran were about 23% and 50%, respectively [3]. Animal models are needed for evaluation of the effect of antihypertensive drugs before using in human trials so we should induce HTN in animal models [2]. There are several types of models for inducing HTN in animals such as surgically induced HTN, endocrine HTN, dietary HTN, neurogenic HTN Chemically Induced HTN, etc. [2]. Also, for a trial of HTN complication's treatment, we need to evaluate it in animal models, and this complication is created when HTN is chronic [2]. Therefore, method induces persistent HTN is suitable in the research study. Glucocorticoids are a subtype of chemically that induced HTN [3]. Dexamethasone (Dexa) is used for the treatment of many diseases such as rheumatologic disorders, allergies, etc. [4]. In spite of its useful effects in treatment, in the long term, it causes HTN, cataracts, osteoporosis, etc. According to the mentioned, in this study we evaluated the persistence of Dexa induced HTN after withdrawing the injection of Dexain 8 & 12 weeks and the comparison of them in an experimental model.

Material and Method

Animals

In this study, adult male Wistar rats weighing 200–250 g (n = 30) were obtained from Pasteur's Institute, Tehran, Iran. Rats were housed five per cage in one colony room at the permanent temperature of 22 ± 1C (50 ± 10% humidity) on a 12-h light/dark cycle with free access to water and food. The experimental protocol for animal care and handling was according to the guidelines of the National Institute of Health guide for the care and use of Laboratory Animals (NIH Publications No. 8023, Revised 1978). The rats were randomly divided into three groups (number of each group = 10); Two groups were injected Dexa for 8 and 12 weeks (Dexa-8, Dexa-12) and the last group served as a control. Before injection of Dexa, three rats were randomly selected from each group to measure their systolic blood pressure (SBP) and heart rate (HR) with the tail-cuff method. Dexa (20μg/kg/day, in a volume of 1 mL/kg) was administered subcutaneously every day, and dosages were adjusted every week according to changes in body weight.

Systolic blood pressure and heart rate measurements

SBP were measured periodically using the tail-cuff method with a photoelectric sensor (NIPREM 546, Cibertec S.A, Madrid, Spain) along the study. During the injection and after withdrawal, measurements were taken every two weeks. For each animal, BP and PR were determined several times in every measurement and data were noted valid if there was a maximum of 10 mm Hg difference between 4 consecutive measurements.

Statistical analysis

All data were expressed as mean ± std. One way ANOVA, followed by Turkey's post hoc test, was used for each group at different time points. In all analyses, the null hypothesis was rejected at the level of >0.05.

Results

Dexa subcutaneously injected to rats and blood pressure rise significantly after 2 weeks (fig 1,2). Blood pressure was rising during injection (Fig1,2) ($p<0.001$).

In the group that received Dexa for 8 weeks, 10 days after stopping of injection, blood pressure significantly remained high in comparison to the control group ($p<0.05$). Measurement of blood pressure in the 21st day showed there isn't a significant difference between groups.

In group that Dexa was injected for 12 weeks, 2, 4 and 8 weeks after stopping injection, the deposit of decrease, blood pressure have a significant difference in comparison to the control group ($p<0.001$).

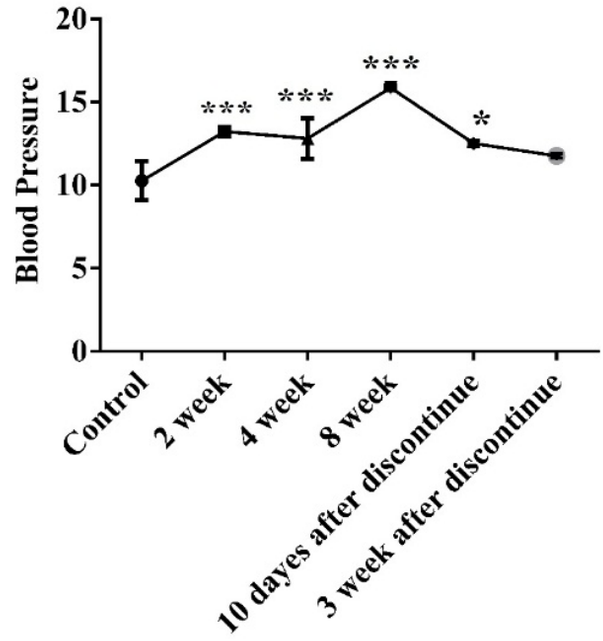

Figure1. during 8 weeks of Dexa injection and injection interrupt, blood pressure measured by tail cuff. The findings show an increase during Dexa injection.

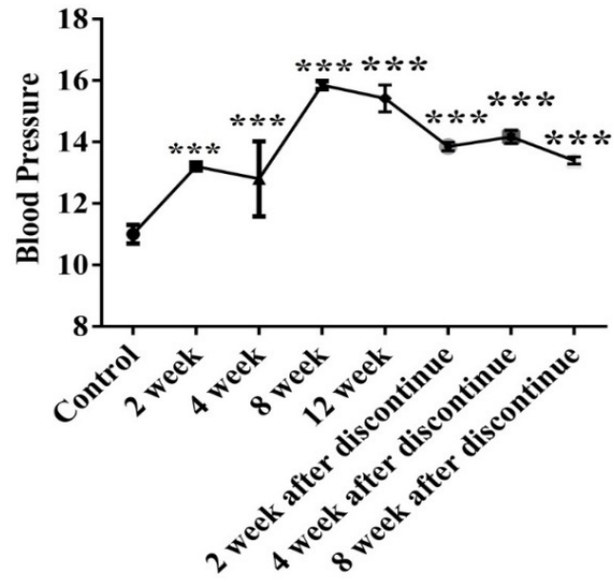

Figure 2. 12 weeks of Dexa injection and injection interrupt, blood pressure measured by tail cuff. The findings show an increase during Dexa injection. In this part of study, the blood pressure remain high much longer.

About heart rate, in Dexa-8 group, the effect of Dexa was not significant with contrast control group (fig.3). In fig.4, in spite of significant rising in heart rate after two and four weeks of injection ($p<0.05$, $p<0.001$), it was not permanent in during of injection and after discontinuation.

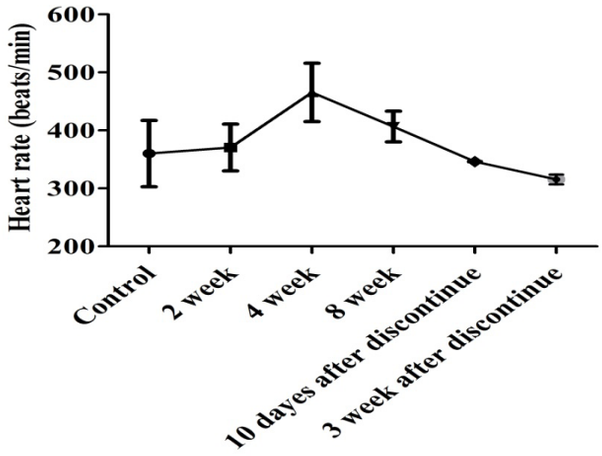

Figure 3. 8 weeks injection of Dexa and injection interrupt. Pulse rate measured by tail cuff.

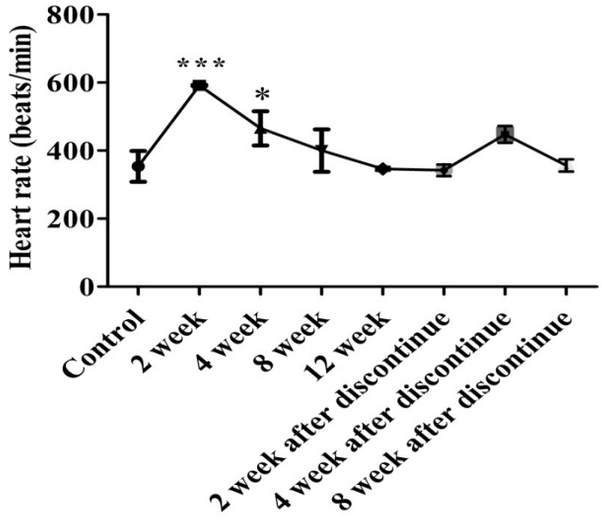

Figure 4. 12 weeks injection of Dexa and injection interrupt. Pulse rate measured by tail cuff (*P < 0.05, ***P < 0.001).

Discussion

There are several types of models for inducing HTN in animals such as surgically induced HTN, endocrine HTN, chemically Induced HTN, etc. [2]. Glucocorticoids are a subtype of chemically Induced HTN method that decreases in serum reactive nitrogen intermediate (NOx) concentration and endothelial nitric oxide synthase (eNOS), mRNA levels in heart, kidney, and liver in mice is accompanied with an injection of it [5-8]. Whiteworth et al. found that Dexa-induced hypertension is not due to its mineralocorticoid activity[9]. Although corticosteroids, especially Dexa, widely used for induction of blood pressure in animal models, there are very few studies about stability and long-term blood pressure in laboratory animals. The administration of Dexa (2.5 mg kg–1 week–1, sc) increased systolic blood pressure by 41 ± 6 mm Hg after 14 days of treatment, associated with elevations of urine volume and fluid intake and loss of body weight [9]. In a study, Dexa significantly increased SBP from 113 ± 4 to 139 ± 6 mmHg. Just administeration of N-Acetyl cysteine did not affect SBP. In the group that treated by NAC + Dexa than that of Dexa-treated rats, SBP was lower significantly [10]. Study of Lexian Hu et al. showed the administration of Dexa increased SBP (104 +/- 3 to 122 +/- 3 mm Hg) and decreased thymus and body weight [11]. In other study, SBP increased from 122 ±5 to 136±3 mm Hg due to 13 days subcutaneously administeration of Dexa [6, 11]. As can be seen, despite the common use of Dexa as a model for blood pressure induction, it is not considered that how long it remains stable? Therefore, it may be high blood pressure returns to normal again, even without any interference. This is important, because the responses of antihypertensive drug may be unrealistic. Therefore, we attempted to investigate this matter in an animal model. In our study, subcutaneously injection of Dexa for 8 & 12 weeks increased blood pressure significantly and because of its persistence is important in research studies that need chronic induced HTN, we decided to evaluate it. We found that 3-month injection of Dexa in rats furthermore that induce HTN to persist for two months after withdrawing of injection whereas injection for two months has less persistency (10days). With due attention to this result, Dexa induced HTN is suggested for studies that need inducing of chronic HTN.

Conclusion

This experimental evidence indicates Dexa subcutaneous injection for a period of 8 & 12 weeks results in a notable blood pressure rise. Furthermore, we evaluate the persistency of this well-known drug because of the importance of chronic induced HTN in researches. Therefore, we establish that Dexa injection for 3 months in rats furthermore that induce HTN to remain for two months after injection withdraw whereas two-month injection has 10days persistency. So, based on these evidence we can conclude that, the persistence of high blood pressure may be based on Dexa injection period.

Conflict of interest

The authors declare no conflict of interest related to the research covered in this article.

References

1. Tripathi K. Antihypertensive drugs, essentials of medical pharmacology. Jaypee brothers medical publishers Pvt. Ltd., New Delhi, 2003. 5: p. 503-4.
2. Sharma P, Vyawahare N, Ladhha A. Preclinical screening models for hypertension in rodents: a review. Pharmacologyonline. 2010; 3: 458-72.
3. Rezazadehkermani M. Epidemiology and heterogeneity of hypertension in Iran: a systematic review. Archives of Iranian Medicine. 2008;11(4):444-52.
4. Beard EL. The American Society of Health System Pharmacists. JONA'S healthcare law, ethics, and regulation. 2001:3(3):78-9.
5. Tonolo G. Chronic low-dose infusions of Dexamethasone in rats: effects on blood pressure, body weight, and plasma atrial natriuretic peptide. Journal of Hypertension. 1988;6(1):25-32.
6. Whitworth JA, Deanna G, John A, Bruce SA. The hypertensive effect of synthetic glucocorticoids in man: the role of sodium and volume. Journal of Hypertension. 1989:7(7):537-49.
7. Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circulation Research. 2003:92(1):81-7.
8. Wallerath T, Gödecke A, Molojavyi A, Li H, Schrader J, Förstermann U, et al. Dexamethasone lacks effect on blood pressure in mice with a disrupted endothelial NO synthase gene. Nitric Oxide. 2004:10(1):36-41.

9. Nasjletti A, Erman A, Cagen LM, Baer PG. Plasma concentrations, renal excretion, and tissue release of prostaglandins in the rat with dexamethasone-induced hypertension. Endocrinology. 1984:114(3):1033-40.
10. Krug S, Zhang Y, Mori TA, Croft KD, Vickers JJ, Langton LK, et al. N-acetylcysteine prevents but does not reverse dexa-induced hypertension. Clinical and Experimental Pharmacology and Physiology. 2008:35(8):979-81.
11. Hu L, Zhang Y, Lim PS, Miao Y, Tan C, McKenzie KU, et al. Apocynin but not L-arginine prevents and reverses Dexamethasone-induced hypertension in the rat. American journal of hypertension. 2006:19(4):413-8.

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