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Research Article

Short-term exposure to dexamethasone promotes autonomic imbalance to the heart before hypertension

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Abstract

Hypertension is one of the chronic side effects of dexamethasone (DEX) treatment; however, almost nothing is known about its acute effects. Therefore, the aim of this study was to investigate the possible mechanisms involved in blood pressure control after acute or short-term DEX treatment in adult animals. Eighty Wistar rats were divided into four groups: C1 and C5, for rats treated with saline for 1 or 5 days, respectively; D1 and D5, for rats treated with DEX for 1 or 5 days, respectively (decadron, 1 mg/kg, *i.p.*). Heart rate was increased in DEX treatment, but arterial pressure and cardiac muscle mass were not altered. Only few and isolated changes on gene expression and protein level of renin-angiotensin system components were observed. Five days of DEX treatment, but not one day, determined an increase in sympathetic component of spectral analysis (+75.93%, $P < .05$) and a significant reduction of parasympathetic component (–18.02%, $P < .05$), which contributed to the autonomic imbalance to the heart (LF/HF, +863.69%). The results of this present study demonstrated, for the first time, that short-term exposure to DEX treatment impairs the autonomic balance to the heart before hypertension, which was independent of renin-angiotensin system. J Am Soc Hypertens 2018;■(■):1–9. © 2018 American Heart Association. All rights reserved.

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Introduction

Dexamethasone (DEX)-induced hypertension is a well-known side effect that occurs after its chronic use in both animals[1–3] and humans.[4,5] In addition to hypertension, this widely used synthetic glucocorticoid may cause body weight (BW) loss (in animals), muscle atrophy, hyperglycemia, peripheral insulin resistance, dyslipidemia, and liver steatosis.[3,6–12]

The mechanisms responsible for DEX-induced hypertension are not well established, but some studies have suggested the role of nitric oxide (NO),[13–16] oxidative stress followed by endothelial dysfunction,[16,17] as well as autonomic nervous system[3,18–20] and renin-angiotensin system (RAS) alterations.[21,22] Recently, our group has demonstrated that chronic DEX treatment determined hypertension associated with decreases in baroreflex activity, without any significant tissue RAS changes.[23]

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Over the last years, most of the studies have analyzed the effects of a prenatal exposure to short-term DEX treatment (or other glucocorticoid, such as betamethasone) to understand the role of glucocorticoids on hypertension. RAS involvement on this type of programmed hypertension is still controversial. Although DEX increased vasoconstriction induced by angiotensin II (Ang II) in sheep's offspring coronary rings,[24] other studies have shown that treatment with AT1 receptor antagonist, in lambs whose mothers were treated with dexamethasone[25] or betamethasone,[26] failed to decrease mean arterial pressure. In addition, it has been shown that treatment of pregnant ewes with DEX or betamethasone throughout gestation provokes hypertension in offspring lambs, which may be associated with hemodynamic and autonomic dysfunctions.[26,27] In addition, in this model of programmed hypertension induced by antenatal treatment with glucocorticoids, sometimes baroreflex alterations may appear before hypertension, which may be associated with cardiac hypertrophy.[27–29]

Our group has shown that acute DEX treatment increases glucose and insulin levels[30] and determines body and muscle weight loss.[11,30] Nevertheless, the autonomic balance to the heart and RAS components expression in the left ventricle (LV) muscle have not been evaluated after acute or short-term DEX treatment in adult rats. Therefore, the aim of this study was to investigate the possible mechanisms involved in blood pressure control after acute or short-term DEX treatment in adult animals. The hypothesis of this study was that acute or short-term DEX treatment may impair autonomic balance to the heart and increase gene/protein level of RAS components in myocardium, which may contribute to the establishment of hypertension.

Methods

Animal Care

For this study, 80 rats (Wistar, 200–250 g) from the Center for Research and Production Facilities of UNESP (Botucatu, SP, Brazil) were used. All rats were kept in cages (five in each) at the Animal Facility Maintenance from Faculty of Science, UNESP at Bauru. Water and food (Biobase, Águas Frias, SC, Brazil) were given *ad libitum*. Rats were maintained in dark-light cycle (12–12 hours) with controlled temperature (22°C). All procedures were approved by the Committee for Ethical Use of Animals of UNESP—São Paulo State University, campus at Bauru (approved protocol # 1434–2014).

Groups and Pharmacological Treatment

Rats were randomly divided into four groups: 1/C1, 20 animals that received saline injection for 1 day *(i.p.)*; 2/D1, 20 animals that received DEX injection for 1 day (Decadron, 1 mg/kg of BW, *i.p.*, at 9 AM); 3/C5, 20 animals that received daily saline injections during 5 days *(i.p.)*; 4/D5, 20 animals that received daily DEX injections (Decadron, 1 mg/kg of BW, *i.p.*, at 9 AM) during 5 days.

Cardiovascular Parameters

On the last day of DEX or saline treatment, rats were anesthetized with tribromoethanol (250 mg/kg, *i.p.*) and a small incision on carotid artery was done to insert a polyethylene catheter. After 24 hours, arterial pressure (AP) and heart rate (HR) were continuously recorded for 30 minutes, in a quiet room, using a pressure transducer (DPT100, Utah Medical Products Inc, Midvale, UT, USA) connected to the artery cannula that sent the signal to an amplifier (Quad Bridge Amp, ADInstruments, NSW, Australia) and then to an acquisition board (Powerlab 4/35, ADInstruments, NSW, Australia) as published.[3] Mean arterial pressure, systolic arterial pressure, diastolic arterial pressure, and HR were derived from pulsatile AP recordings.

Spectral Analysis

Cardiac pulse interval (PI) from long recordings (15–30 minutes) was processed by a computer software (Labchart v7.0, ADInstruments, NSW, Australia) as previously published,[3] which uses an algorithm that detects cycle-to-cycle inflection points in the pulsatile AP signal. Thus, HR variability analysis within frequency domain was processed using DIAS software (DPM, from University of São Paulo, Brazil, CardioSeries V2.4, http://www.danielpenteado.com) by a non-parametric fast Fourier transform algorithm. From these data, it was obtained a low frequency band power (LF, 0.20–0.75 Hz) and high frequency band power (HF, 0.75–3.0 Hz), which are related to sympathetic and parasympathetic activity, respectively. Results were expressed as normalized units (nu) and, to assess the sympathovagal balance, the LF/HF ratio of PI variability was calculated.[31,32]

Tissue Harvesting

After cardiovascular parameters measurements, all animals were euthanized by an overload of xylazine hydrochloride (20 mg/kg, *i.p.*; Anasedan, Paulínia, SP, Brazil) and ketamine hydrochloride (160 mg/kg, *i.p.;* Dopalen, Paulínia, SP, Brazil). LV muscle was removed, cleaned, and immediately weighed. One sample of the heart was stored at –80°C for protein analysis and another portion was kept in RNAlater tissue storage reagent (Qiagen, 21 Strasse, Germany) and maintained at −80°C until RNA extraction, as previously published.[12]