



Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Chronic stress and Rosiglitazone increase indices of vascular stiffness in male rats

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HIGHLIGHTS

- Chronic variable stress (CVS) is associated with increased pulse pressure.
- CVS is associated with increased collagen deposition in the aortic adventitia.
- Treatment with Rosiglitazone during CVS additionally increases pulse pressure.

ARTICLE INFO

Article history:

Received 11 January 2016

Received in revised form 14 March 2016

Accepted 26 March 2016

Available online xxx

Keywords:

Stress

HPA

Autonomic

Metabolic disease

Cardiovascular disease

PPAR

ABSTRACT

Prolonged and/or frequent exposure to psychological stress responses may lead to deterioration of organs and tissues, predisposing to disease. In agreement with this, chronic psychosocial stress is linked to greater cardiovascular risk, including increased incidence of atherosclerosis, myocardial ischemia, coronary heart disease, and death. Thus the association between stress and cardiovascular dysfunction represents an important node for therapeutic intervention in cardiovascular disease. Here we report that 2 weeks of chronic variable stress (CVS) increased indices of vascular stiffness, including increased collagen deposition in the aortic adventitia and increased resting pulse pressure, in male rats. Thus CVS may represent a useful rodent model for stress-associated CVD, especially for aging populations for which widening pulse pressure is a well-known risk factor. Additionally, we report that the thiazolidinedione Rosiglitazone (RSG) blunts chronic stress-associated increases in circulating corticosterone. Despite this, RSG was not protective against adverse cardiovascular outcomes associated with chronic stress. Rather RSG itself is associated with increased pulse pressure, and this is exacerbated by chronic stress—highlighting that chronic stress may represent an additional contributor to RSG-associated cardiovascular risk.

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<http://dx.doi.org/10.1016/j.physbeh.2016.03.031>

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Please cite this article as: M.L. Goodson, et al., Chronic stress and Rosiglitazone increase indices of vascular stiffness in male rats, *Physiol Behav* (2016), <http://dx.doi.org/10.1016/j.physbeh.2016.03.031>

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1. Introduction

A large literature links chronic stress to cardiovascular morbidity and mortality in human populations (reviewed by [1–3]). This relationship between stress and cardiovascular dysfunction represents an important target for the development of therapeutic interventions, since cardiovascular disease (CVD) remains the leading cause of death worldwide [4].

In response to an acute psychological stressor, both sympathetic nervous system and hypothalamic-pituitary-adrenocortical (HPA) axis activity is increased, facilitating the mobilization and distribution of fuels. When an individual experiences chronic stress, frequent and/or persistent exposure to these physiological responses over a period of time is thought to create wear and tear on organs and tissues, predisposing to disease [5]. Consequently, we reasoned that pharmacological interventions that blunt sympathetic and hormonal responses to acute stress might provide effective therapy against chronic stress-associated cardiovascular dysfunction.

The peroxisome-proliferator activated receptor- γ (PPAR γ) is a nuclear receptor that is activated by fatty acids and fat metabolites, to regulate the transcription of genes involved in lipid and glucose metabolism. Pharmacological agonists of PPAR γ include the thiazolidinedione (TZD) class of insulin-sensitizing drugs. Our recent work demonstrates that, in addition to their well-known effects on glucose homeostasis, the TZD Rosiglitazone also effectively blunts both the tachycardic and glucocorticoid response to acute psychological stress in rats [6]. In the present study we tested the hypothesis that chronic psychological stress induces cardiovascular dysfunction, which may be abrogated by concurrent treatment with RSG.

2. Materials and methods

2.1. Animals

The Institutional Animal Care and Use Committees at the University of Cincinnati and the University of California, Davis approved all animal protocols. Male Long-Evans rats (~275 g) were obtained from Harlan Labs (Indianapolis, IN), and allowed to acclimate to the vivarium for at least one week prior to surgery or other experimental procedures. Rats were singly-housed with ad libitum access to water and standard rat chow, and maintained on a 12:12 light:dark cycle with lights on at 06:00 h and off at 18:00 h.

2.2. Drugs

RSG (Cayman Chemicals, Ann Arbor, MI) was suspended in 0.2% methylcellulose (Sigma Chemical Co., St. Louis, MO) in water at a concentration of 1 mg/mL, and administered at 10 mg/kg body weight per day by oral gavage. This dose was chosen because it is therapeutic for glycemic control in rats [7] and because our recent work demonstrates

that this dose is effective to blunt both corticosterone and heart rate responses to acute restraint stress in rats [6].

2.3. Surgical procedures

Rats were implanted with radiotelemetry transmitters (Data Sciences International, St. Paul, MN) as previously described [6,8]. Briefly, animals were anesthetized using inhaled isoflurane anesthesia. The descending aorta was exposed via an abdominal incision, allowing implantation of a catheter extending from the transmitter. The catheter was secured with tissue adhesive (Vetbond; 3M Animal Care Products, St. Paul, MN) and a cellulose patch. The capsule was sutured to the abdominal musculature, the abdominal musculature was sutured, and wound clips were applied to the skin. Rats recovered for at least 1 week and wound clips were removed prior to beginning the experiments.

2.4. Cardiovascular parameters

Cardiovascular parameters [heart rate, mean arterial pressure (MAP), and systolic, diastolic and pulse pressures] and general locomotor activity were continuously recorded. AM and PM baseline telemetric measurements were collected for 5 days prior to any intervention, and for each rat changes in these variables were calculated relative to the average of the 5 day baseline. Morning (AM) measurements were collected between 06:30 and 08:30 h. Night (PM) measurements were collected from 18:00 to 06:00 h the next day. Animals were undisturbed by animal care or research staff during these time periods.

2.5. Chronic variable stress (CVS)

CVS consisted of twice-daily exposure to one of several stressors, presented in a randomized order between 10:00 and 15:00 h, for 15 days. Stressors included hypoxia (8% O₂, 92% N₂ for 30 min), cold room (4 °C for 1 h), shaker platform (100 rpm for 1 h), restraint (in a well-ventilated Plexiglas tube for 30 min), overnight housing in small cages normally used to house mice, and overnight housing in cages with damp bedding. Unstressed control rats were disturbed only for daily administration of RSG or VEH and for regular husbandry unless otherwise noted.

In cohort 1, rats were first outfitted with telemetry devices and allowed to fully recover from surgery. We collected 5 days of baseline cardiovascular data, and then divided the individuals evenly into 4 treatment groups, matched for baseline MAP: 1) unstressed control rats receiving vehicle (CON-VEH), 2) unstressed control rats receiving RSG (CON-RSG), 3) rats subjected to CVS receiving vehicle (CVS-VEH), and 4) rats subjected to CVS receiving RSG (CVS-RSG). Rats received 4 days of RSG or VEH by gavage prior to the first day of CVS.

In cohort 2, rats were divided evenly into the same 4 treatment groups and subjected to CVS and daily oral gavage, but without the use of telemetry devices: 1) unstressed control rats receiving vehicle

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