Vascular Pharmacology 82 (2016) 41–50

Contents lists available at ScienceDirect

Vascular Pharmacology

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

Review

Glucocorticoid-induced fetal origins of adult hypertension: Association with epigenetic events☆,☆☆

M. Akhtar Anwar [a], Alaaeldin I. Saleh [a], Reem Al Olabi [b], Tuqa S. Al Shehabi [c], Ali H. Eid [a,d,*]

[a] Department of Biological and Environmental Sciences, Qatar University, Doha, Qatar
[b] Qatar Biomedical Research Institute, Doha, Qatar
[c] Department of Health Sciences, Qatar University, Doha, Qatar
[d] Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

ARTICLE INFO

Article history:
Received 10 December 2015
Received in revised form 15 February 2016
Accepted 18 February 2016
Available online 20 February 2016

Keywords:
Cardiovascular disease
Hypertension
Embryonic programming
Epigenetics
Pharmacogenomics
Glucocorticoids

ABSTRACT

Hypertension is a predominant risk factor for cardiovascular diseases and a major health care burden. Accumulating epidemiological and experimental evidence suggest that adult-onset hypertension may have its origins during early development. Upon exposure to glucocorticoids, the fetus develops hypertension, and the offspring may be programmed to continue the hypertensive trajectory into adulthood. Elevated oxidative stress and deranged nitric oxide system are not only hallmarks of adult hypertension but are also observed earlier in life. Endothelial dysfunction and remodeling of the vasculature, which are robustly associated with increased incidence of hypertension, are likely to have been pre-programmed during fetal life. Apparently, genomic, non-genomic, and epigenomic factors play a significant role in the development of hypertension, including glucocorticoid-driven effects on blood pressure. In this review, we discuss the involvement of the aforementioned participants in the pathophysiology of hypertension and suggest therapeutic opportunities for targeting epigenome modifiers, potentially for personalized medicine.

Contents

☆ This publication was made possible by grant no. NPRP 4-571-3-171 from the Qatar National Research Fund (a member of Qatar Foundation). The Statements made herein are solely the responsibility of the authors.
☆☆ This grant was awarded to Ali H. Eid.
* Corresponding author at: Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut, PO-Box 11-0236, Beirut, Lebanon; and Department of Biological and Environmental Sciences, College of Arts and Sciences, Qatar University, P. O. Box 2713, Doha, Qatar.
E-mail addresses: ae81@qu.edu.qa, ali.eid@qu.edu.qa (A.H. Eid).

http://dx.doi.org/10.1016/j.vph.2016.02.002
1537-1891/

1. Introduction

Cardiovascular diseases (CVDs) remain the major cause of morbidity and mortality [1]. Of all CVDs, hypertension is the most predominant risk factor for myocardial infarction, stroke, aortic aneurysm, and atherosclerosis among other diseases. Hypertension is divided into two categories, essential and secondary. Glucocorticoid-induced elevation in blood pressure is classified as secondary hypertension and is a principal risk factor for cardiovascular-related diseases [2–4,1]. However, the etiology of hypertension is far from clear. In a significant number of hypertensive patients, blood pressure is not successfully managed in spite of the diverse and extensive therapeutic armaments, even with polypharmacy/polytherapy available to physicians [5]. Recent inroads to our understanding of epigenetic processes have advanced our knowledge on their involvement in a broad array of disorders, including cardiovascular diseases [6], cancer [7], and neurocognitive conditions [8]. Hence, it is feasible that the lack of response to drugs may be due to epigenetic mechanisms [9,10].

Glucocorticoids are characterized by a broad spectrum of homeostatic and pathophysiological functions (metabolism, vascular tone, anti-inflammatory, immune, volume, and ion regulation in the kidney, reproduction) [3,11]. Due to their lipophilic nature, they are inherently able to access any given organ, tissue, or cell within the body; this is illustrated by their ability as steroid lipids to freely traverse the plasma membrane, including the blood brain barrier. In essence, their influence may take two pathways, either immediate non-receptor-driven effects or receptor-mediated influences or possibly both. The current dogma for cortisol-mediated elevation in blood pressure is that of endothelial cell dysfunction; the main protagonists for this endothelial derangement being the enhanced reactive oxygen species [12] and reduced nitric oxide (NO) bioavailability [12]. A consequence of augmented vascular oxidative stress is topological alterations of luminal wall along the length of vascular tree [13]. This remodeling is indeed linked to "poorer" prognosis for hypertension [14].

Fetal origins of adult hypertension have been widely documented [15,16]. Again, ROS and altered nitric oxide system appear to be important signaling components in the priming of the fetus during development of hypertension. Furthermore, epigenomic modifications are important determinants of programming of hypertension from early uterine environment to extra-uterine life. Therefore, in this review, we examine these determinants particularly in glucocorticoid-induced hypertension. We also highlight where further studies are required to cement the thesis put forward in our review.

2. Hypothalamic–pituitary–adrenal axis (HPA axis) and glucocorticoids

Cortisol (corticosterone in rodents) is synthesized in the adrenocortical cells of zona fasciculata and is under circadian control [17]. Various signals trigger the paraventricular nucleus in the hypothalamus to secrete corticotropin-releasing hormone (CRH), which in turn stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland [2]. ACTH stimulates the release of cortisol by binding to ACTH receptors present on the surface of the adrenocortical cells [3]. The whole mechanism is a finely orchestrated homeostatic symphony involving interplay between the different components of the HPA-axis, leading to a finale in cortisol secretion. Glucocorticoids (GCs), in a feedback loop, control the release of CRH and ACTH by binding onto receptors within the hypothalamus and pituitary gland (Fig. 1). Thus, the action of glucocorticoids is regulated by its corresponding receptor [17] as well as non-receptor mechanisms [18].

In utero glucocorticoid manipulation programs (primes) the HPA axis to adverse long-lasting consequences associated with aging [15,19–21]. Hence, excessive exposure to glucocorticoids has a drastic impact on birth weight, behavior, development of organogenesis, and ultimately, blood pressure [15,22,23].

Interestingly, local, extra-adrenal production of glucocorticoids may act synergistically to augment the effects of the circulating pool of GCs [24,25]. This may have a dramatic influence on the vasculature, among other tissues/organs, to enhance the glucocorticoid-induced hypertension. However, GC excess is normally regulated by the glucocorticoid receptor (GR) and the regulatory enzymes (11beta-hydroxysteroid dehydrogenases; 11β-HSDs).

3. 11β-HSD-related pathophysiology

Cortisone, another steroid hormone, is considered the inactive form of cortisol owing to its lower glucocorticoid activity [26]. The interconversion of cortisone and cortisol is performed by the isozymes 11β-HSD [26,27]. 11β-HSD 1 is responsible of converting cortisone to cortisol, whereas 11β-HSD 2 triggers the reverse reaction by inactivating cortisol [26,27]. Importantly, the highest concentration of these enzymes is located in resistance arteries compared to other regions of the vascular tree [28]. Thus, they likely contribute to the regulation of vascular resistance, and hence blood pressure.

Several studies link glucocorticoid-mediated actions to the regulation of vascular tone [29–31]. It has been reported that a decrease in 11β-HSD 2 activity leads to potentiation of vascular tone upon exposure to catecholamines and angiotensin II [32]. Additionally, in 11β-HSD 2-deficient mice, endothelial dysfunction is prominent, indicative of impaired NO synthesis and diminished guanylate cyclase activity. Interestingly, this endothelial deranged homeostasis enhances the norepinephrine-mediated aortic contraction [33]. Likewise, in several phenotypes of metabolic syndrome, inhibition of 11β-HSD 1 activity alleviates blood pressure, insulin resistance, and dyslipidemia [34].

Mutations in 11β-HSD 2 have been reported. In one instance, a syndrome called apparent mineralocorticoid excess (AME) ensues when a missense mutation in 11β-HSD 2 takes place. This mutation causes an inhibition in the conversion of cortisol to cortisone, which then leads to an excessive build-up of cortisol in the kidney. As a consequence, robust activation of mineralocorticoid receptors occurs, evoking severe hypertension, hypokalemia, and hypernatremia [35–39].

4. Fetal origins of GC hypertension

Epidemiological and experimental studies show that low birth weight is associated with elevated blood pressure in childhood and adult life [40,41]. This has led to the suggestion that adverse events (malnutrition, exposure to GCs) at critical periods of early development are a prelude to increased cardiovascular and other diseases in the offspring's later life. This is referred to as fetal origin of adult-onset diseases or the Barker hypothesis [15]. Several lines of evidence lend support to this association. For example, raised fasting plasma cortisol levels has been shown to strongly associate with low birth weight [19]. Equally importantly, low birth weight was also found to be associated with high aldosterone levels [42].

Interestingly, this fetal origin hypothesis would theoretically predict that high birth weight (HBW) individuals would have a lower risk for cardio-metabolic diseases than normal or low birth weight ones. This has been suggested to be counter-intuitive since overweight and/or overnutrition in various stages of an individual's life would be expected to increase the risk of metabolic diseases [43]. Importantly, a recent systematic review and meta-analysis has found that blood pressure in HBW individuals is higher than the normal birth weight ones, but that is only during childhood [43]. Indeed, this study reports that in older subjects, HBW was associated with lower blood pressure [43]. Another meta-analysis study further supported these findings of an inverse relation between birth weight and blood pressure in individuals aged 35 years or older [44]. Taken together, these meta-analyses suggest a "catch-down" phenomenon. This phenomenon is in fact common in babies born large, where a postnatal "catch-down" in height and weight has been previously reported [45,46].