Brain, Behavior, and Immunity 50 (2015) 31–38

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Beta-adrenergic receptor mediated inflammation control by monocytes is associated with blood pressure and risk factors for cardiovascular disease

Suzi Hong [a,b,*], Stoyan Dimitrov [a], Tiefu Cheng [a], Laura Redwine [a], Christopher Pruitt [a], Paul J. Mills [a,b], Michael G. Ziegler [c], J. Michael Green [a], Farah Shaikh [a], Kathleen Wilson [a]

[a] Department of Psychiatry, University of California San Diego, USA
[b] Department of Family Medicine and Public Health, University of California San Diego, USA
[c] Department of Medicine, University of California San Diego, USA

ARTICLE INFO

Article history:
Received 7 May 2015
Received in revised form 10 August 2015
Accepted 11 August 2015
Available online 20 August 2015

Keywords:
Beta adrenergic receptor
Blood pressure
Depression
Fasting glucose
Intracellular TNF levels
Lipids
Monocytes
Prehypertension

ABSTRACT

Overwhelming data indicate that individuals with even mildly elevated blood pressure (BP) are at great risk for developing clinical hypertension and future cardiovascular disease (CVD). There remains a lack of consensus regarding treatment strategies for mildly elevated BP, termed prehypertension, and the knowledge of pathophysiology and mechanisms of its clinical outcomes remains limited. Our primary aim was to investigate βAR-mediated inflammation control (BARIC) responses of blood monocytes to isoproterenol (Iso) in relation to BP and CVD risk factors, including obesity, depressive mood, fasting glucose, triglycerides, and cholesterol levels in the 64 prehypertensive compared to 84 individuals with normal BP. BARIC was determined by measuring the degree of inhibition in lipopolysaccharides-stimulated monocytic intracellular TNF production by ex vivo Iso treatment (10^{-8} M). Depressive mood was assessed by Beck Depression Inventory (BDI). Fasting metabolic and lipid panels were assessed, and plasma levels of inflammatory cytokines TNF, IL-1β, IL-6 were measured in a subset to confirm proinflammatory state of prehypertensive participants. Prehypertensive participants were older, heavier, included more men, and presented higher levels of fasting glucose, triglycerides, cholesterol, and plasma TNF compared to normotensive participants (p's < .05). BARIC was significantly attenuated in the prehypertensive compared to normotensive group (p < .05). BARIC was negatively associated with systolic BP, diastolic BP, age, BMI, fasting glucose, triglycerides, total and low density cholesterol levels, and somatic depressive symptoms in all participants (p's < .0001 to .05). However, among the prehypertensive individuals BARIC was positively associated with SBP even after controlling for the covariates (age, gender, race, BMI, glucose and lipid panel, somatic BDI scores) (p < .05). This differing nature of the BARIC–SBP relationship between the two BP groups may be attributed to moderating factors such as cardiorespiratory fitness or depressive symptoms that could not be clearly deciphered in this current study. Nonetheless, our findings indicate the associations between inflammation dysregulation mediated by sympathoadrenal activation and BP that is observable even among individuals with normal to mildly elevated BP. BARIC may be a useful and sensitive indicator of elevated risk for vascular inflammatory disease that can be detected even at lower BP levels, especially given its associations with traditional CVD risk factors and the critical role of monocytes in atherogenic processes.

1. Introduction

It has been over a decade since the 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has emphasized that "…beginning at 115/75 mmHg, cardiovascular disease (CVD) risk doubles for each increment of 20/10 mmHg" and that individuals with even mildly elevated blood pressure (BP; systolic BP, SBP 121–139 mmHg and/or diastolic BP, DBP 81–89 mmHg termed "prehypertension") are prone to a progressive rise in BP and CVD risk (Chobanian et al., 2003). Population studies worldwide report high prevalence of prehypertension: 30–50% of adult populations with a higher rate for men (Chockalingam et al., 2005; Choi et al., 2006; Greenlund et al., 2004; Julius et al., 2006; Lee et al., 2006; Tsai et al., 2005),

* Corresponding author at: Department of Psychiatry, University of California San Diego, 9500 Gilman Dr. MC0804, La Jolla, CA 92093-0804, USA.
E-mail address: suzihong@ucsd.edu (S. Hong).

http://dx.doi.org/10.1016/j.bbi.2015.08.012
0889-1591/

as high as 57% of adolescents (Israeli et al., 2006), and almost 30% of young children (Grotto et al., 2006). Forty percent of prehypertensive, middle-aged individuals developed hypertension within two years, and nearly two thirds of them progressed to hypertension in four years when left untreated (Julius et al., 2006). Progression rates from prehypertension to hypertension in older age are higher among African Americans (Greenlund et al., 2004). Prehypertension is also related to future CVD, even after controlling for other risk factors (Liszka et al., 2005) and specifically associated with an increased risk (relative risk of 3.5) for myocardial infarction and developing coronary artery disease within 9–10 years (Qureshi et al., 2005). Clinical guidelines based on the JNC 7 strongly recommended treatment or intervention even for mild BP elevation based on these findings, including a pharmacological intervention if necessary. Clinicians also agree that classifying individuals as prehypertensive is of little value without clarification of justified and individualized intervention plans (Moser et al., 2006). While, the recently-released JNC 8 report (James et al., 2014) updated the guidelines that set BP goals at higher levels for management of high BP (e.g., to treat hypertensive persons over 60 years of age to a BP goal of less than 150/90 mmHg). Without clear characterization of pathophysiology of prehypertension and uncovering its underlying mechanisms, implementation of efficacious therapeutics is difficult.

The associations of hypertension with markers of systemic and vascular inflammation have been reported by our group (Hong et al., 2004, 2005; Hong and Mills, 2008; Mills et al., 2003) and many others (Kop, 2003; Kop and Gottdiener, 2005; Hwang et al., 1997). Elevated inflammation is linked to current and future cardiovascular pathology (see Frostegård, 2013; Ross, 1999 for review). Prehypertensive individuals exhibited 7% lower total antioxidant capacity levels and 15% higher oxidized LDL levels compared to normotensive participants, implying atherosclerotic processes that may initiate at the level of mild BP elevation (Chrysohoou et al., 2004). In spite of many epidemiological studies, reporting an increasing incidence of prehypertension worldwide and risk for future CVD development, studies of underlying vascular inflammatory process and its implications in future CVD in prehypertension remain sparse.

More studies are needed to uncover the degree and pathways of the impact of modest BP elevations on vascular inflammatory and atherogenic processes in order for better risk assessment for future CVD. Migration and infiltration of inflammatory immune cells, such as monocytes into the vascular endothelium, is a key process in the pathogenesis of vascular inflammatory disease (Savoia and Schiffrin, 2007). Monocyte mobilization, recruitment, infiltration, and inflammatory cytokine production (such as tumor necrosis factor, TNF) are prominently involved in atherosclerotic lesions (Branen et al., 2004; McKellar et al., 2009; Skoog et al., 2002). The impact of sympathetic activation in accelerating hypertension and cardiovascular pathology is well-documented (Abboud, 1982; Goldstein, 1983; Weber and Drayer, 1982). Thus, investigations of sympathoadrenal regulation of monocytes/macrophages would shed light on pathophysiology of vascular inflammation. Beta 2 ($\beta 2$) adrenergic receptor (AR) numbers on circulating lymphocytes are greater in hypertensive individuals, and AR density is positively correlated with BP (Brodde et al., 1984a,b; Fitzgerald et al., 1983; Middeke et al., 1983). But, βARs are also shown to be desensitized in hypertensive individuals (Grassi et al., 2010), which points to the complexity in sympathoadrenal regulatory mechanisms involved in end-organ responses.

Adrenergic receptors ($\alpha 1$, $\alpha 2$, $\beta 1$, and $\beta 2$ subtypes) are shown to be expressed on various immune cell types, including monocytes and play a major role in regulating diverse cellular activities, including inflammatory responses (Dimitrov et al., 2013; Heine et al., 2012; Hong et al., 2014). The literature on leukocytes' inflammatory responses upon AR engagement or catecholamine stimulation is largely variable such that catecholamines induce both pro- (e.g., Flierl et al., 2008; Kavelaars et al., 1997; Torres et al., 2005) and anti-inflammatory (e.g., Hu et al., 1991; van der Poll et al., 1994) responses by immune cells. These seemingly contradictory effects of catecholamines on inflammatory responses appear to depend on a number of factors (see Padro and Sanders, 2014 for review), including AR subtype (Hanke et al., 2012; Heijnen et al., 1996), AR agonist concentrations (e.g., Szelényi et al., 2000), and the timing of AR engagement in relation to antigen stimulation (Sanders, 2012). We have previously reported that βAR-mediated mobilization responses of proinflammatory monocytes was attenuated among prehypertensive individuals (Dimitrov et al., 2013). We also reported a significant associations of diminished monocytes' βAR responsivity to isoproterenol (Iso) in TNF production with elevated systemic inflammatory cytokine levels and adiposity (Hong et al., 2014).

The primary aim of the present study was to investigate the extent to which blood monocytes suppressed LPS-stimulated TNF production under β-ARs engagement using Iso among individuals with normal and prehypertensive BP. We hypothesized that prehypertensive individuals would exhibit diminished monocytic responses to the inhibitory effect of Iso in TNF production compared to normotensive individuals. Furthermore, we aimed to investigate and hypothesized that this β-AR-mediated inflammation control (namely, "BARIC") would be associated with BP and traditional CVD risk factors, including obesity, lipid profile, and fasting glucose levels. As the secondary investigation of the study, the association between β-AR-mediated inflammation control and depressive mood was examined, given the well-documented depression-CVD association. Given that there has been limited neuro-immune characterization of prehypertension, our study to gain insight into the sympathoadrenal-immune link in relation to traditional CVD risk factors in prehypertension would shed light on risk for future CVD and potential therapeutics.

2. Materials and methods

2.1. Participants

All participants gave informed consent to the protocol, which was approved by the University of California, San Diego Human Research Protection Program. One hundred forty-eight healthy, non-smoking men and women between the ages of 18–65 years with blood pressure range of normal to prehypertension (SBP < 145 and/or DBP < 95 mmHg to account for BP elevations during office visits) were included in this study from a parent trial of prehypertension and neuro-immune activation. To confirm eligibility, all subjects underwent clinical laboratory blood tests for liver, metabolic, lipid, and thyroid panels. Individuals who reported a current diagnosis or a history of heart, liver, or renal disease, diabetes, psychiatric and mood disorders, severe asthma, ongoing inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, lupus), acute illness, and current pregnancy were excluded. Criteria for exclusion also included current use of any anti-hypertensive medications, anti-inflammatory medications, or other medications that are known to influence the immune or neuroendocrine parameters of interest (e.g., beta blockers), current drug or alcohol abuse, and smoking within 6 months of the enrollment in the study.

2.2. Procedure

Blood was collected between 8 and 10 am through an intravenous catheter inserted into an antecubital vein using minimal tourniquet. Participants fasted for 12 h except for drinking plain