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ROLE OF LEPTIN IN HYPERTENSION: A SHORT REVIEW

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ABSTRACT

Leptin is an adipocytokine produced mainly in white adipose tissues though also produced in the brown adipose tissues and in a variety of body organs. It is 167-amino acid protein present in our body in free form and bound with proteins. Leptin is involved in the pathogenesis of hypertension and cardiovascular diseases, regulates food intake and energy expenditure and fat stores and helps performing several other physiological and pathophysiological processes. Some of the recent studies in human and animal studies explain the involvement of leptin in hypertension. However, most of the information about leptin-sympathetic and leptin-resistance actions has been predicted on the basis of in vitro and animal studies, and hence, it is essential to have data from human studies.

Key Words: Leptin, adipocytokine, hypertension.

INTRODUCTION

The literature reveals that leptin is involved in influencing a variety of physiological and patho-physiological processes (Adamiak *et al*., 2016; Gavello *et al*., 2016; Li *et al*., 2016; Quarta *et al*., 2016). Leptin and other adipokines are involved in the pathogenesis of disorders including obesity, arterial hypertension, atherosclerosis, diabetes mellitus, heart failure and hyperlipidemia (Bełtowski, 2006) and some of these substances especially leptins are considered both dependent predictors (for obesity and other factors) (Momose *et al*., 1999; Itoh*et al*., 2002; Haque *et al*., 2006; Nakamura *et al*., 2009; Atwa *et al*., 2014; Vaněčková*et al*., 2014; Kerimkulova *et al*., 2014) and independent predictors (for endothelial and immune factors) (Kazumi *et al*., 1999; Schutte *et al*., 2005; Dubey and Hesong, 2006; Thomopoulos *et al*., 2009; Bełtowski, 2006; Kartal *et al*., 2008; Olszaneckа*et al*., 2010; Bełtowski, 2012;; Karbowska and Kochan, 2012; Allison *et al*., 2013; Rahma *et al*., 2013) for endothelial function/ dysfunction in normotensives. Concentration and association of leptin with cardiovascular risks in patients with coronary artery disease have been investigated in a recent study (Bickel *et al*., 2016).

On the other hand, controversial results for the association of adipokines have also been documented. e.g. acute administration of leptin showing no effect on blood pressure (Bełtowski, 2006). Most of the information about leptin-sympathetic and leptin-resistance actions has been predicted on the bases of in vitro and animal studies, and it is essential to have data from human studies (Correia and Haynes, 2004). However, there are reports showing contradictory results for the regulation of blood pressure and vice versa. e.g. among the subjects with higher blood pressure, neither the association of leptin with systolic blood pressure nor with diastolic blood pressure was found statistically significant (Wada *et al*., 2006). Some of the recent studies in human and animal studies explain the involvement of leptin in hypertension (Hurr and Young, 2016; Paleczny *et al*., 2016; Wu *et al*., 2016; Xue *et al*., 2016). However, further well controlled studies are required to carry out in human subjects following the investigations obtained in animal studies.

LEPTIN

Leptin is considered as a significant factor in normal and pathological conditions (Adamiak*et al*., 2016; Ayeser *et al*., 2016; Bickel *et al*., 2016; Ciresi *et al*., 2016; Gavello *et al*.,2016; Li *et al*., 2016; Quarta *et al*., 2016). The advent of recombinant leptin / leptin analog metreleptin are now used for the treatment of congenital leptin deficiency and lipodystrophy. Other involvements/ functions suggest that adipokines have the potential to be used as biomarkers in a variety of diseases (Blüher and Mantzoros, 2015; Ayeser *et al*., 2016).

Molecular weight of leptin is a 16-kDa protein and it is an adipocytokine produced mainly in white adipose tissues though also produced in the brown adipose tissues and in a variety of body organs (Margetic *et al*., 2002). It is 167-amino acid protein present in our body in free form and bound with proteins (Sinha *et al*., 1996). It is involved in the pathogenesis of hypertension and cardiovascular diseases, regulates food intake and energy expenditure (Bełtowski, 2006) and fat stores and performs several other functions (Maffei *et al*., 1995; Quarta *et al*., 2016). Plasma leptin level is proportional to the amount of adipose tissue and it is increased markedly in obese people (Bełtowski, 2006; Quarta *et al*., 2016).

In view of the significant role of leptin, one of the prestigious Prize in Saudi Arabia- 'King Faisal International Prize' was awarded on the recognition of research on leptin (KFF – KFIP – Winners, 2013) beside several other prizes (News-Medical, 2009; The Lasker Foundation, 2010; BBVA Foundation, 2012).

LEPTIN AND HYPERTENSION

The recent findings explain the role of leptin in hypertension in clinical and experimental studies (Hurr and Young, 2016; Paleczny *et al*., 2016; Wu *et al*., 2016; Xue *et al*., 2016). Association of leptin, hypertension and obesity studied in a Kyrgyz group by weight, height, waist/ hip circumference, BMI, blood pressure, fasting plasma glucose and serum leptin measurements showed elevated leptin level associated with the higher risk of hypertension and correlated with BMI and waist circumference, systolic blood pressure and diastolic blood pressure (Kerimkulova *et al*., 2014). Leptin levels obtained were similar in obese African and Caucasian women, but leptin is associated favourably to vascular function in obese Caucasians, but not in obese Africans (Schutte*et al*., 2005). Increased serum leptin was found to be associated with tachycardia and increases in both systolic and diastolic blood pressure in obesity through complex mechanisms (Haque *et al*., 2006).

It has been investigated that the abnormal variations in the leptin and other adipokines can lead to the clinical characteristics frequently recognized in resistant hypertension (de Faria *et al*., 2014). Hence, any approach to regulate adipokines might be fruitful for the management of resistant hypertension (de Faria *et al*., 2014). Leptin is considered important in regulating the endothelial functions (e.g. hypertension and atherosclerosis) in normal and abnormal conditions (Bełtowski, 2012).

Normal and pathological conditions have been interpreted involving leptin causing the endothelium dependent vasorelaxation and impairment in vasodilatory effect respectively and a major cause leading to arterial hypertension (Bełtowski, 2012).

Another investigation (Dubey and Hesong, 2006) shows that atherogenic mechanism of leptin and the beneficial role of statins is related via the involvement of leptin in increasing the oxidative stress and blood pressure. Free leptin has similar leptin related vascular impairment as it was found almost equally increased in masked as well as sustained hypertension in nonobese subjects (Thomopoulos *et al*., 2009). Plasma leptin levels are important in the regulation of blood pressure in women, differential distribution/ activity of leptin in women and men and gender differences in hypertension (Ma *et al*., 2009).

In the area of cardiovascular studies, leptin is considered as important in understanding the regulation of blood pressure and pathophysiology of arterial hypertension irrespective of obesity and body adiposity both in normotensives and in hypertensives (Bełtowski, 2006). Hyperleptinemia independent of body fat or body mass index may be a regulator of arterial pressure (Kazumi *et al*., 1999).

Administration of leptin showing no effect on blood pressure, might be due to its concomitant stimulation to the sympathetic nervous system and involvement of natriuresis and nitric oxide (NO)-dependent vasorelaxation, and the elevation of blood pressure by chronic hyperleptinemia is probably due to impairment of acute depressor effects and appearance of sympathetic nervous system-independent pressor effects additionally, e.g. oxidative stress, more production of endothelin, NO deficiency, and increased renal Na reabsorption (Bełtowski, 2006).

Much of the information about leptin-sympathetic and leptin-resistance actions have been predicted on the bases of in vitro and animal studies, it is essential to have data from humans studies (Correia and Haynes, 2004). Sympathetic actions of leptin explain a relevant mechanism for the regulation of blood pressure and leptin resistance. However, disturbance in the intracellular signaling pathways and resistance of specific leptin-responsive neural networks provide a better approach to understand selective leptin resistance (Correia and Haynes, 2004).

Regulation of blood pressure, sexual maturation and angiogenesis relate to possible involvement of leptin as it is predicted from experimental studies that leptin represents hematopoietic factor via the long isoform of leptin receptor belonging to cytokine receptors group, though not investigated in clinical studies. This necessitates exploring the role of leptin in various phases of hematological diseases and during the treatment of these diseases (Haluzík *et al*., 2000). It has been investigated that serum leptin levels increase in patients with hypertensive intracerebral haemorrhage (Zhao *et al*., 2012).

Since leptin is involved in sympathetic control of blood pressure, it was tried to confirm whether the loss of leptin is involved in hypotension in patients with multiple system atrophy frequently exhibiting orthostatic hypotension (Ozawa *et al*., 2014). However, results did not prove that. The circulating leptin level preserved and hypotension was found to occur independent of the involvement of leptin in patients with multiple system atrophy (Ozawa *et al*., 2014).

Assessment of the relationship between adipocytokine levels and blood pressure, serum lipid and glucose in middle-aged perimenopausal women having essential hypertension, showed the strongest predictors as waist circumference and serum leptin levels, and apparently the association of adiponectin and resistin concentration with

blood pressure values could not be obtained, that also indicates that hypertensive postmenopausal females showing increased leptin concentration have important role in the pathogenesis of hypertension, independent of BMI (Olszanecka *et al*., 2010).

In view of the contradictory results on the association of leptin with dyslipidemia, a study comprising serum leptin, body height, weight, BMI waist circumference, hip circumference, blood pressure, plasma glucose (fasting), lipid profile (total cholesterol , triglycerides, high-density lipoprotein, cholesterol, low-density lipoprotein cholesterol), showed leptin positively correlating with BMI, waist circumference and triglycerides in both sexes of Kyrgyz and with total cholesterol in Kyrgyz males (Mirrakhimov *et al*., 2014).

For investigating the relationship between the elevation in blood pressure and serum leptin due to the influence of noise in work place, it was found that systolic blood pressure and diastolic blood pressure had a significant correlation with leptin levels compared to the control possibly under the influence of sympathetic nervous system and involvement of leptin in diverse cardiovascular actions. (Rahma *et al*., 2013).

Determination of serum leptin, adiponectin, and resistin, and correlations of these adipokines with insulin resistance and other risk factors for cardiovascular disease in patients with Acanthosis nigricans, showed significant variation between Acanthosis nigricans patients and obese controls in serum leptin, adiponectin, and resistin. Significant positive correlations between serum leptin and glucose, insulin, BMI, low-density lipoprotein and cholesterol, and significant negative correlations between adiponectin and insulin, cholesterol, BMI, and leptin in patients with Acanthosis nigricans were obtained (Atwa *et al*., 2014).

The angiotensin II serum levels in lean females and angiotensin II and leptin as well in obese subjects were noticed as strong predictor of blood pressure (Al-Hazimi and Syiamic, 2004). Leptin may play a prominent role in the pathophysiology of hypertensives with obesity and after weight loss (Itoh *et al*., 2002). Serum leptin has significant gender based differences and it correlates positively with body fat. However, it is still not verified whether leptin levels are independently related to eating behavior, physical activity, serum lipids and blood pressure (Momose *et al*., 1999).

Associations found among blood pressure and leptin, resistin, tumor necrosis factor-α (TNFα), and total adiponectin in a multiethnic study of atherosclerosis, higher level of leptin was found significantly associated with higher systolic, diastolic, mean arterial and pulse pressures as well as higher odds for hypertension (Allison *et al*., 2013). The results indicated that: leptin and hypertension strongly associated in men, though not varying by BMI, race/ethnic group, or smoking status; adiponectin, resistin and TNFα not associated independently with blood pressure / hypertension; higher serum leptin, but not resistin, adiponectin, or TNFα, associated with higher blood pressure / higher odds of hypertension, independent of risk factors, other adipokines and anthropometric measures (Allison *et al*., 2013).

It was found that obstructive sleep apnea hypopnea syndrome might affect blood pressure independently, particularly DBP, after waking up, and serum leptin may be the independent correlate of hypertension in such conditions (Huang *et al*., 2010).

Increased serum leptin levels are significantly related with left ventricular hypertrophy independently of level of blood pressure and body mass index (Kartal *et al*., 2008). Circulating leptin is related to body fatness, but the hypertensive influence of leptin can be modified by physical exercise and fitness (Sabatier *et al*., 2008). Hyperleptinemia was found a significant risk factor for high blood pressure in elderly individuals mainly the male subjects (Mendoza-Núñez *et al*., 2006). Among the subjects with higher blood pressure, however, neither the association of leptin with systolic blood pressure nor with diastolic blood pressure was found statistically significant (Wada *et al*., 2006).

One study involving the hypertensives revealed significant positive correlation for leptinvs body mass index and leptinvs body adiposity index whereas the normotensives showedleptin positively correlating with body adiposity index and negatively correlating with waist-to-hip ratio, adiponectin negatively correlating with waist-to-hip ratio , and resistin negatively correlating with waist-to-hip ratio. In general, the obese hypertensives showed visceral obesity and leptin associated with hypertension (Stepien *et al*., 2014).

CONCLUSION

Considering the recent findings about the role of leptin in hypertension (Hurr and Young, 2016; Paleczny *et al*., 2016; Wu *et al*., 2016; Xue *et al*., 2016), a variety of physiological and pathophysiological processes can be explained. However, most of the information about leptin-sympathetic and leptin-resistance actions have been predicted on the basis of in vitro and animal studies, and it is essential to have data from human studies (Correia and Haynes, 2004).

There are reports showing contradictory results for the role of adipokines in the regulation of blood pressure and vice versa. e.g. among the subjects with higher blood pressure, neither the association of leptin with systolic blood

pressure nor with diastolic blood pressure was found statistically significant (Wada *et al*., 2006), that emphasizes for collection of data by well organized way and interpretation of well controlled data from human subjects, since the data obtained merely from animal studies cannot serve solely for interpreting the intricate role of leptin in hypertension and other disorders.

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