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Review

Riboflavin, *MTHFR* genotype and blood pressure: A personalized approach to prevention and treatment of hypertension

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ABSTRACT

Hypertension is the leading risk factor contributing to mortality worldwide, primarily from cardiovascular disease (CVD), while effective treatment of hypertension is proven to reduce CVD events. Along with the well recognized nutrition and lifestyle determinants, genetic factors are implicated in the development and progression of hypertension. In recent years genome-wide association studies have identified a region near the gene encoding the folate-metabolizing enzyme methylenetetrahydrofolate reductase (MTHFR) among eight loci associated with blood pressure. Epidemiological studies, which provide a separate line of evidence to link this gene with blood pressure, show that the 677C→T polymorphism in *MTHFR* increases the risk of hypertension by 24–87% and CVD by up to 40%, albeit with a large geographical variation in the extent of excess disease risk suggestive of a gene–environment interaction. Emerging evidence indicates that the relevant environmental factor may be riboflavin, the MTHFR co-factor, via a novel and genotype-specific effect on blood pressure. Randomized trials conducted in hypertensive patients (with and without overt CVD) pre-screened for this polymorphism show that targeted riboflavin supplementation in homozygous individuals (*MTHFR* 677TT genotype) lowers systolic blood pressure by 6 to 13 mmHg, independently of the effect of antihypertensive drugs. The latest evidence, that the blood pressure phenotype associated with this polymorphism is modifiable by riboflavin, has important clinical and public health implications. For hypertensive patients, riboflavin supplementation can offer a non-drug treatment to effectively lower blood pressure in those identified with the *MTHFR* 677TT genotype. For sub-populations worldwide with this genotype, better riboflavin status may prevent or delay the development of high blood pressure. Thus riboflavin, targeted at those homozygous for a common polymorphism in *MTHFR*, may offer a personalized treatment or preventative strategy for hypertension. Further investigations of this novel gene–nutrient interaction in relation to blood pressure, hypertension and hypertension in pregnancy are required.

Abbreviations: CVD, cardiovascular disease; EGRac, erythrocyte glutathione reductase activation coefficient; eNOS, endothelial nitric oxide synthase; FAD, flavin adenine dinucleotide; GWAS, Genome Wide Association Studies; MTHFR, methylenetetrahydrofolate reductase; NO, nitric oxide.

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Contents

1. Introduction

Hypertension is the leading risk factor contributing to cardiovascular disease (CVD) and to mortality worldwide, while interventions to lower blood pressure, even by small amounts, are proven to decrease cardiovascular risk (World Health Organization, 2013; Mozaffarian et al., 2016). Multiple lifestyle and genetic factors are thought to contribute to the development and progression of hypertension, and there have been recent calls for more individual-focused approaches to lower blood pressure and thus improve cardiovascular health (Mozaffarian et al., 2016). Evidence from both GWAS and epidemiological studies implicates the gene encoding the folate-metabolizing enzyme methylenetetrahydrofolate reductase (MTHFR) in hypertension (Ehret et al., 2011; Yang et al., 2014). Notably, the common 677C→T polymorphism in *MTHFR* is associated with an increased risk of not only hypertension (Yang et al., 2014a), but also CVD especially stroke (Holmes et al., 2011). The geographical variability in the extent of excess cardiovascular risk owing to this polymorphism points to a gene–environment interaction, and recent evidence suggests that riboflavin, the MTHFR cofactor (as FAD), may play an important modulating role in this relationship via a novel effect on blood pressure. This review will explore the available evidence that the underrecognized blood pressure phenotype associated with the *MTHFR* 677C→T polymorphism is modifiable by riboflavin status and the potential mechanisms that may explain this gene–nutrient interactive effect. The public health implications and translation of this novel role of riboflavin to healthcare will also be considered.

2. Hypertension – a global public health issue

2.1. The burden of high blood pressure

Hypertension, defined as a systolic/diastolic blood pressure of 140/90 mmHg or greater, affects an estimated 1 billion people globally (World Health Organization, 2013). It is the leading risk factor contributing to mortality worldwide and accounts for over 9 million deaths annually, primarily from cardiovascular disease (CVD) (Lim et al., 2012). It is estimated that there is a doubling in the risk of cardiovascular diseases for each 20 mmHg rise in systolic blood pressure, or 10 mmHg rise in diastolic blood pressure (Lewington et al., 2002). The economic costs of hypertension are substantial, with direct and indirect healthcare costs estimated at $48.6 billion for the U.S. alone, and predicted to increase to $274 billion by 2030 (Mozaffarian et al., 2016).

Several potentially modifiable lifestyle factors, including poor diet, higher BMI, smoking, excessive alcohol consumption and lack of physical activity, can all contribute to the development and progression of hypertension (Yusuf et al., 2004). Genetic factors are also well recognized to play an important role. The emergence of genome-wide association studies (GWAS) in the last decade has enabled specific genes linked with blood pressure to be identified (Newton-Cheh et al, 2009; Levy et al., 2009) and these are discussed below (Section 3.1).

2.2. Benefits of blood pressure-lowering

Effective lowering of blood pressure is proven to be highly beneficial in reducing cardiovascular mortality (Gaziano et al, 2009; Falaschetti et al., 2014; Mozaffarian et al., 2016). Blood pressure can be effectively lowered by antihypertensive pharmacological agents (often prescribed in combinations), including calcium channel blockers, thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. Although generally found to be much less effective, lifestyle and dietary modifications are also a focus of blood pressure management, with interventions aimed at weight reduction, increased physical activity, decreased alcohol consumption, dietary sodium restriction and/or a whole diet approach (Appel et al., 1997, 2003). Of note, recent evi-

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