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Review Article

Riboflavin Lowers Blood Pressure: A Review of a Novel Gene-nutrient Interaction

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ABSTRACT

Hypertension, defined as a systolic/diastolic blood pressure of 140/90 mmHg or greater, is estimated to carry a three-fold increased risk of developing cardiovascular disease (CVD). Evidence from genome-wide association studies has identified an association between blood pressure and the gene encoding the folate-metabolising enzyme, methylenetetrahydrofolate reductase (MTHFR). Recent meta-analyses of observational studies show an increased risk of hypertension in people homozygous for the 677C→T polymorphism in MTHFR. Riboflavin in the form of flavin adenine dinucleotide (FAD) acts as a cofactor for MTHFR, and the variant enzyme is known from molecular studies to become inactive for having an increased propensity to dissociate from FAD. Our findings revealed that CVD patients with *MTHFR* 677TT genotype (compared to CC or CT genotype) have significantly higher blood pressure, and that blood pressure was highly responsive to intervention with riboflavin, resulting in significant lowering, specifically in the TT genotype group. Further investigations confirmed this gene-nutrient interaction in hypertensive patients (with and without overt CVD), and showed that the blood pressure lowering effect of riboflavin in the TT genotype group was independent of antihypertensive drug use. Although the precise mechanism linking this polymorphism to hypertension remains to be established, it would appear that the biological perturbation, which leads to higher blood pressure in individuals with MTHFR 677TT genotype, is modifiable by correcting the variant MTHFR enzyme through enhancing riboflavin status. Thus riboflavin, targeted specifically at this genetically at-risk group, may offer a personalised non-drug approach to managing hypertension.

Keywords: Blood pressure, Hypertension, MTHFR, Personalised medicine, Riboflavin

Introduction

Hypertension, defined as a systolic/diastolic blood pressure (SBP/DBP) ≥140/90mmHg is the leading risk factor for mortality worldwide (1), and is responsible for an estimated 8 million premature deaths per year (2). Drug and lifestyle strategies, which lower BP, even by modest amounts, significantly decrease cardiovascular disease (CVD) risk without any evidence of a threshold down to BP values as low as 115/75 mmHg (3). The exact patho-physiology of hypertension remains unclear, and multiple lifestyle and genetic risk factors have been identified. Recent genome-wide association studies have identified several genetic loci associated with BP variation (4, 5). One such locus is near the gene encoding methylenetetrahydrofolate (MTHFR), the folate metabolising enzyme required for the formation of 5-methyltetrahydrofolate. One particular variant of this gene (677 C→T polymorphism) has received much attention as the main genetic determinant of homocysteine concentrations (6, 7), and has also been independently associated with an increased risk of CVDs and particularly stroke (7, 8). The frequency of MTHFR 677TT genotype is reported to be 10% worldwide, ranging from 4%-18% in the United States, to 20% in northern China, and 32% in Mexico (9). Evidence from meta-analyses suggests that individuals with the homozygous mutant TT

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genotype are at 14-16% increased risk of coronary heart disease compared to those with the CC genotype (10, 11) although there is much geographical variation in the extent of excess risk of CVD owing to this polymorphism. More recently, this polymorphism has been associated with hypertension (12-15). The homozygous mutant (TT) genotype expresses an MTHFR enzyme with decreased activity (6). Riboflavin (Vitamin B2) is required as a cofactor (flavin adenine dinucleotide; FAD) for MTHFR, and the decreased enzyme activity in individuals with the TT genotype results from a greater propensity for loss of FAD (16, 17). Supplementation with riboflavin lowers homocysteine concentrations, specifically in individuals with the TT genotype (18), and therefore, appears to overcome the increased tendency for loss of FAD from the active site.

Blood pressure control, riboflavin and the MTHFR 677C→T polymorphism

More recently, we were the first to report a novel role for riboflavin in modulating BP, specifically in individuals with the MTHFR 677TT genotype. Supplementation with riboflavin can lower BP in hypertensive individuals with the TT genotype but not in those with the CC or CT genotype (19). In this placebo-controlled study, premature CVD patients were randomised within all three genotype groups to receive either a low dose of riboflavin (1.6 mg/d) supplement or placebo over a 16-week intervention period. Intervention with riboflavin decreased systolic (SBP) by 13mmHg and diastolic BP (DBP) by 8mmHg in individuals with the TT genotype while no BP response was observed in those with the CC or CT genotype. In this study, BP at baseline was significantly higher in patients with the TT genotype compared with those with the CC and CT genotypes; an effect which was most pronounced in those with the lowest baseline riboflavin status as determined by the functional biomarker of riboflavin status, erythrocyte glutathione reductase activation coefficient (EGRac). Some four years after the original study, a follow-up randomised trial (20) reinvestigated the effect of riboflavin (1.6mg/d) supplementation on BP in the same cohort of high-risk CVD patients but this time with the riboflavin and placebo groups reversed. During the 4-year interval between the two riboflavin interventions (in 2004 and 2008), there were marked changes in the prescribed antihypertensive therapy following a major review of the National Institute for Health and Clinical Excellence (NICE) guidelines in the United Kingdom; in which β-blockers were replaced by ACE inhibitors as a first-line treatment for hypertension, and a switch from mono-therapy to poly-therapy was advocated. Even with the change in drug treatments, the genotype-specific BP-lowering effect of riboflavin was evident with significant reductions in SBP (9.2mmHg, P=0.001) and DBP (6.0mmHg, P=0.003) observed when the original intervention groups were reversed. Most recently, the responsiveness of BP to riboflavin intervention was investigated in a group of hypertensive individuals who did not have overt CVD and were pre-screened to select those with the MTHFR 677TT genotype (n=91). Although almost all participants in this genotype group were prescribed antihypertensive therapy (typically involving a combination of 3 or more drugs), less than one third achieved target BP (≤140/90mmHg) at baseline. Riboflavin supplementation, however, lowered SBP (by 5.6mmHg, P=0.033) and improved BP control rates. Supplementation with riboflavin resulted in 57% of participants achieving target BP compared with only 30% in the placebo group. All patients continued to receive their prescribed medication throughout the intervention period. Therefore, the BP lowering effect of low-dose riboflavin was confirmed, and was shown to be applicable to hypertensive individuals generally with the TT genotype and not confined to high-risk CVD patients (21).

Mechanism of action

Despite taking three or more anti-hypertensive medications at baseline, 60% of the participants in the study of Wilson et al. (21) failed to achieve target BP (≤140/90 mmHg). Therefore, it is evident that the BP-lowering effect of riboflavin can occur in the face of a wide variation in drug treatments; however, the precise mechanism to explain the role of MTHFR-riboflavin interaction in lowering BP is not clear. A plausible mechanism of action might be related to the potent vasodilator nitric oxide as bioavailability of nitric oxide is directly related to endothelial function and indirectly to the mode of

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action of a range of BP lowering drugs (22). Concentrations of 5-methyltetrahydrofolate (the product of MTHFR reaction) in vascular tissue are associated with nitric oxide regulation and endothelial function, and are lower in patients with the MTHFR 677TT genotype (23). By stabilising the variant MTHFR enzyme, it is possible that riboflavin supplementation could restore 5-methyltetrahydrofolate concentrations in vascular cells, and improve nitric oxide availability, which, in turn, would improve endothelial function, and lower BP.

An alternative or complementary mechanism could involve an imbalance in the non-methylated folate derivatives in the endothelial cells of individuals with the MTHFR 677TT genotype, and thereby could impact negatively on eNOS coupling. Bagley and Selhub (24) found that there was an accumulation of formylated tetrahydrofolates in the red blood cells of TT individuals while only 5-MTHF was found in the red blood cells of individuals with the CC genotype. One could speculate that if a similar accumulation of 10-formyl THF occurs in the endothelial cell, such accumulation might affect the adjacent pathways of folate metabolism, and could, in turn, affect eNOS activity. Improving eNOS coupling with riboflavin, either by increasing 5-MTHF or by ameliorating the imbalance with respect to methylated versus non-methylated THF, specifically in individuals with the TT genotype (relative to their non-TT counterparts of the same age), should lower BP irrespective of the BP lowering drug(s) employed. Such improvement in eNOS coupling may offer an explanation for our finding of BP-lowering by riboflavin supplementation in individuals with the TT genotype being treated with a variety of BP-lowering medications (19-21).

Conclusion

In conclusion, MTHFR 677TT genotype has been shown to be an important determinant of hypertension and related co-morbidities in several populations. Given the genotype-specific responsiveness to BP lowering by riboflavin intervention demonstrated in three separate trials from our centre, it is possible that the large reported geographical variations in the extent of excess CVD risk owing to this polymorphism may relate not only to compromised folate status but may also be the result of differences in prevailing riboflavin status among different populations. Overall, there is convincing evidence of the potential for a personalised approach to hypertension treatment whereby riboflavin intervention could be targeted at those people sharing this common genetic factor.

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