Original Communication

B-Vitamins, Methylenetetrahydrofolate Reductase (MTHFR) and Hypertension

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Abstract: Hypertension is a leading risk factor for cardiovascular disease (CVD) and stroke. A common polymorphism in the gene encoding the enzyme methylenetetrahydrofolate reductase (MTHFR), previously identified as the main genetic determinant of elevated homocysteine concentration and also recognized as a risk factor for CVD, appears to be independently associated with hypertension. The B-vitamin riboflavin is required as a cofactor by MTHFR and recent evidence suggests it may have a role in modulating blood pressure, specifically in those with the homozygous mutant MTHFR 677 TT genotype. If studies confirm that this genetic predisposition to hypertension is correctable by low-dose riboflavin, the findings could have important implications for the management of hypertension given that the frequency of this polymorphism ranges from 3 to 32 % worldwide.

Key words: riboflavin, B vitamins, hypertension, MTHFR.

Introduction

Hypertension (i.e. a blood pressure of 140/90 mmHg or greater) is responsible for 14 % of deaths worldwide (7.6 million) and is a major independent risk factor for cardiovascular disease (CVD) accounting for approximately 50 % of the global risk for ischemic heart disease and stroke [1]. Extensive epidemiological and clinical data support a continuous and linear relationship between blood pressure and mortality across the entire blood pressure range, starting from 115/75 mmHg, with each increment of 20 mmHg systolic blood pressure and 10 mmHg diastolic blood pressure associated with a doubling in cardiovascular risk [2]. The benefits of lowering blood pressure are well documented; a modest lowering of 2 mmHg in systolic blood pressure has been reported to decrease vascular risk by 10 % while a 10 mmHg lowering reduces risk of death from stroke by as much as 40 % [3]. Despite the wide availability of clinically effective antihypertensive drugs, however, and the fact that 10 % of global healthcare costs are directed towards treating hypertension [4], worldwide hypertension control rates remain poor.

The exact cause of hypertension remains unclear although it is recognized as being multifactorial with factors including age, dietary factors, and obesity all known to play an important role in its etiology. Evi-

dence suggests that between 30 to 60 % of the variability associated with blood pressure is inherited [5] and in recent years much attention has focused on investigating genetic variants linked with hypertension. This paper focuses on one such variant, namely the C677T polymorphism in the gene encoding the folate-metabolizing enzyme methylenetetrahydrofolate reductase (MTHFR) and its association with hypertension. The modulating role of the B-vitamin riboflavin on blood pressure, in individuals with this genetic variant, is considered specifically.

Methylenetetrahydrofolate reductase (MTHFR)

MTHFR is a key enzyme in the metabolism of homocysteine, an elevated concentration of which is considered to be a risk factor for CVD and particularly stroke [6]. The reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which in turn acts as a methyl donor in the conversion of homocysteine to methionine, is MTHFR-dependent (Figure 1). A common variant, the C677T polymorphism in the gene coding for this folate-metabolizing enzyme, with a reported frequency of between 3 to 32 % in populations worldwide [7], has been identified as the most important genetic risk factor for elevated homocysteine. In those homozygous for the polymorphism (TT genotype), MTHFR activity is reduced, leading to elevated homocysteine concentrations, particularly in those with low folate status. A second B vitamin, riboflavin, in its co-enzymatic form FAD (flavin adenine dinucleotide), is required as a co-factor for MTHFR. Work conducted previously using recombinant human MTHFR suggests that enhancing riboflavin status would stabilize the variant enzyme, resulting in enhanced MTHFR activity leading to a decrease in homocysteine concentration [8]. In a previous study conducted at this center we demonstrated that intervention with low-dose riboflavin resulted in a marked lowering in homocysteine, specifically in people with the TT genotype [9].

In addition to being recognized as the main genetic determinant of homocysteine, evidence from several meta-analyses provides convincing data that individuals with (compared to those without) this genetic factor have a 14 to 21 % increased risk of CVD [10–12]. More recently the C677T polymorphism has been associated with hypertension, albeit the evidence has not been entirely consistent [13,14]. To the best of our knowledge, a total of only three meta-analyses to date have analyzed this polymorphism in association with hypertension. Kosmas *et al.* [15] reported a significant association between the polymorphism and blood pressure in women with pregnancy-related hypertension, which was strongest in those with diastolic hypertension (> 110 mmHg) [15]. A second meta-analysis published a number of years later included patients with hypertension generally as well as those with hypertension in pregnancy from 26 studies conducted in Asian and Caucasian populations, which confirmed a significant association in both populations, although similar to the previous investigation a large degree of heterogeneity across different studies was observed [16]. In an attempt to address the issue of heterogeneity the most recent meta-analysis to be published

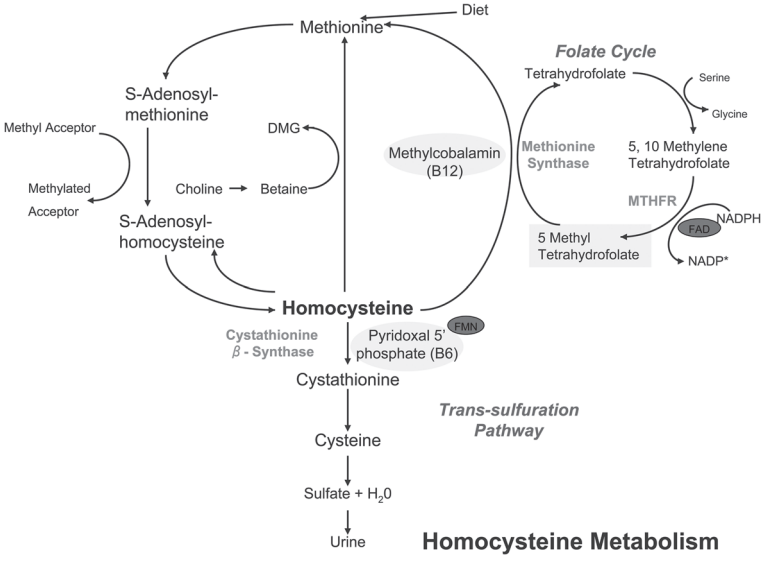

Figure 1: Homocysteine metabolism.

focused specifically on Chinese population studies and reported a consistent and significantly increased risk of developing hypertension and gestational hypertension in carriers of the T allele [17].

B vitamins and blood pressure

The blood pressure-lowering effect of B-vitamin intervention has been examined in both healthy people and hypertensive patients, however results have been generally disappointing [18,19]. A modest, but significant blood pressure (BP) response was noted in response to high-dose folic acid (5 mg/day) in a study involving 130 siblings of patients with premature atherothrombosis [18]. Of note, however, no effect on blood pressure was observed in the Vitamin Intervention Stroke Prevention study, which involved 3,680 patients with cerebral infarct [20]. This lack of response to either high- or low-dose B-vitamin intervention over a two-year period was observed despite the fact that a significant decrease of 2.3 μmol in homocysteine concentration was achieved in those assigned to the high-dose B-vitamin combination (2.5 mg/folic acid, 25 mg pyridoxine, and 0.4 mg of cobalamin). Similarly McMahon and colleagues [21] failed to show any blood pressure-lowering effect of B vitamins in a cohort of healthy elderly adults in response to intervention with high-dose B vitamins over a two-year period. Of note, however, none of these studies considered the effect of B-vitamin intervention on blood pressure specifically in individuals with the TT genotype and none of the interventions included riboflavin. Given the genotype-specific effect of riboflavin reported previously by our group, we recently hypothesized that enhancing riboflavin status would influence blood pressure in hypertensive people with the TT genotype.

MTHFR, blood pressure, and riboflavin

In a placebo-controlled study conducted in 181 premature CVD patents (pre-screened for the C677T polymorphism in MTHFR, from a larger cohort of 404), the blood pressure response to low-dose riboflavin (1.6 mg/day) was investigated [22]. Some 49 patients with the TT genotype and a similar number of age-sex matched patients with heterozygous (CT) or wild type (CC) genotypes, who were randomized within each genotype group to treatment or placebo, completed the 16-week intervention. Consistent with previous reports, baseline blood pressure was significantly higher in patients with the TT genotype (Figure 2). At baseline blood pressure was found to be significantly higher in those with the TT compared with the other genotypes. When the influence of riboflavin status (as determined by the biomarker erythrocyte glutathione reductase activation co-efficient; EGRac) on baseline blood pressure across the genotype groups was considered, it was noted among those with generally lower riboflavin status (i.e. EGRac value above the median), mean blood pressure was 16 mmHg higher in the TT versus the CC genotype groups. Of greater note a clinically and statistically significant lowering of 13.4 mmHg (systolic) and 7.5 mmHg (diastolic) in blood pressure was achieved in response to the 16-week intervention in those with the TT genotype, with no effect observed in either of the other two genotype groups (Figure 2). Furthermore, the decrease in blood pressure achieved appeared to be independent of antihypertensive medication use, which was reported in 82 % of those who participated in the study [22].

This highly selected group of patients was subsequently invited to participate in a follow-up study four years after the completion of the original investigation. In those with the TT genotype that had originally

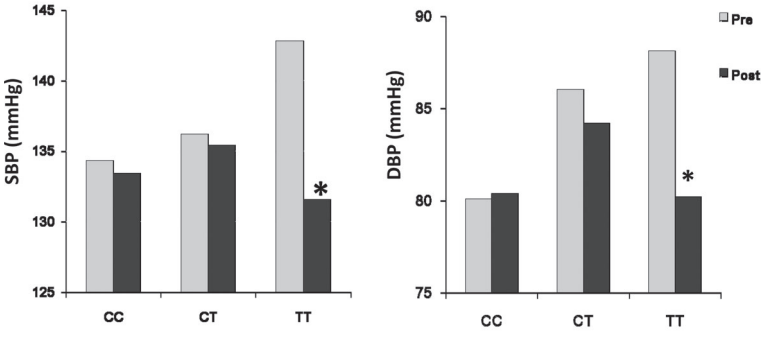

Figure 2: Blood pressure lowering response to riboflavin intervention (1.6 mg/day) by MTHFR genotype (Horigan et *al.,* 2010).

received riboflavin, mean blood pressure was found to have returned to a level not significantly different from that originally reported prior to intervention. A follow-up intervention (in the TT genotype group only) in which the original treatment groups were reversed, confirmed the blood pressure-lowering effect of riboflavin in this genetically at-risk cohort [23]. Both of these intervention studies were conducted in a cohort of high-risk CVD patients. Further studies are required to confirm the blood-pressure lowering effect of riboflavin in this genotype group among hypertensive patients and in the general population. Studies are also needed to explore potential mechanisms, which are currently not known, linking MTHFR, blood pressure, and riboflavin; however it is possible that the potent vasodilator nitric oxide may be involved [24].

Conclusion

Given the prevalence of the MTHFR 677 TT genotype (3–32 % worldwide), the clinical and economic implications for governments, health authorities, and the food industry, of confirming that this relatively common genetic factor is associated with suboptimal control of BP and is correctable by riboflavin are considerable. Further large-scale randomized trials are needed to confirm these findings in hypertensive patients generally and in the population at large.

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