Interaction of Riboflavin with MTHFR Genotype in relation to Hypertension

Helene McNulty
Northern Ireland Centre for Food & Health (NICHE)
ulster.ac.uk
Riboflavin, MTHFR Genotype and Hypertension

This talk will address

- Hypertension
- MTHFR genotype and hypertension
- Riboflavin as a personalised nutrition strategy for
  - Treating hypertension
  - Preventing hypertension
- Impact
High BP (Hypertension) – a global health concern

Mortality due to global risk factors

Lopez et al. 2006 Lancet 367,1747-57
Hypertension

- The major risk factor for cardiovascular disease, and stroke in particular

- Defined as a blood pressure (BP) of greater than 140/90 mmHg

- Multiple lifestyle, nutritional and genetic factors known to affect BP

- Antihypertensive drugs are highly effective yet hypertension remains a global problem

- Dietary approaches to lower BP
  - Weight loss; salt reduction; DASH diet; alcohol
## Nutrition and Lifestyle factors targeted to reduce blood pressure

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Modified from Chobanian *et al.* 2003 JNC 7 report
A number of genetic variants appear to contribute modestly to blood pressure variability

The **MTHFR gene** is among 8 genetic loci linked to the variation in blood pressure in Genome-Wide Association Studies (GWAS studies)\(^1,^2\)

Genome-wide association study identifies eight loci associated with blood pressure

Christopher Newton-Cheh\textsuperscript{1–3,94*}, Toby Johnson\textsuperscript{4–6,94}, Vesela Gateva\textsuperscript{7,94}, Martin D Tobin\textsuperscript{8,94}, Murielle Bochud\textsuperscript{5}, Lachlan Coin\textsuperscript{9}, Samer S Najjar\textsuperscript{10}, Jing Hua Zhao\textsuperscript{11,12}, Simon C Heath\textsuperscript{13}, Susana Eyheramendy\textsuperscript{14,15}, Konstantinos Papadakis\textsuperscript{16}, Benjamin F Voight\textsuperscript{1,3}, Laura J Scott\textsuperscript{7}, Feng Zhang\textsuperscript{17}, Martin Farrall\textsuperscript{18,19}, Toshiko Tanaka\textsuperscript{20,21}, Chris Wallace\textsuperscript{22–24}, John C Chambers\textsuperscript{9}, Kay-Tee Khaw\textsuperscript{12,25}, Peter Nilsson\textsuperscript{26}, Pim van der Harst\textsuperscript{27}, Silvia Polidoro\textsuperscript{28}, Diederick E Grobbee\textsuperscript{29}, N Charlotte Onland-Moret\textsuperscript{29,30}, Michiel L Bots\textsuperscript{29}, Louise V Wain\textsuperscript{8}, Katherine S Elliott\textsuperscript{19}, Alexander Teumer\textsuperscript{31}, Jian’an Luan\textsuperscript{11}, Gavin Lucas\textsuperscript{32}, Johanna Kuusisto\textsuperscript{33}, Paul R Burton\textsuperscript{8}, David Hadley\textsuperscript{16}, Wendy L McArdle\textsuperscript{34}, Wellcome Trust Case Control Consortium\textsuperscript{93}, Morris Brown\textsuperscript{35}, Anna Dominiczak\textsuperscript{36}, Stephen J Newhouse\textsuperscript{22,23}, Nilesh J Samani\textsuperscript{37}, John Webster\textsuperscript{38}, Eleftheria Zeggini\textsuperscript{19,39}, Jacques S Beckmann\textsuperscript{4,40},

Roles of folate and related B-vitamins in one-carbon metabolism
Folate and related B vitamins

• Required for one-carbon metabolism

• Have a major metabolic role in methylation processes

• Prevent homocysteine accumulation

• Health benefits may
  – relate to their homocysteine-lowering effects or
  – be independent of homocysteine
All countries in blue fortify flour with iron and folic acid except Australia which does not include iron, and Venezuela, the United Kingdom, the Philippines, and Trinidad and Tobago which fortify with iron only and do not include folic acid.
Decline in stroke related mortality in the US and Canada

Yang et al 2006 Circulation;113:1335-43
Homocysteine

\[ \text{S-Adenosyl-homocysteine} \rightarrow \text{S-Adenosyl-methionine} \]

Methyl Acceptor

Methylated Acceptor

\[ \text{Methyl Acceptor} \rightarrow \text{Methylated Acceptor} \]

\[ \text{S-Adenosyl-homocysteine} \rightarrow \text{Cystathionine} \]

\[ \text{Cystathionine} \rightarrow \text{Cysteine} \]

\[ \text{Cysteine} \rightarrow \text{Sulfate} + \text{H}_2\text{O} \]

\[ \text{Sulfate} + \text{H}_2\text{O} \rightarrow \text{Urine} \]

\[ \text{Cysteine} \rightarrow \text{Cystathionine} \]

\[ \text{Cystathionine} \rightarrow \text{Homocysteine} \]

\[ \text{Homocysteine} \rightarrow \text{Methionine} \]

\[ \text{Methionine} \rightarrow \text{Tetrahydrofolate} \]

\[ \text{Tetrahydrofolate} \rightarrow \text{5,10 Methylene Tetrahydrofolate} \]

\[ \text{5,10 Methylene Tetrahydrofolate} \rightarrow \text{Methionine Synthase} \]

\[ \text{Methionine Synthase} \rightarrow \text{B12} \]

\[ \text{B12} \rightarrow \text{MTHFR} \]

\[ \text{MTHFR} \rightarrow \text{5 Methyl THF} \]

\[ \text{NADPH} \rightarrow \text{NADP}^* \]

\[ \text{B2} \rightarrow \text{B12} \]

\[ \text{B2} \rightarrow \text{NADPH} \]

\[ \text{NADPH} \rightarrow \text{NADP}^* \]

\[ \text{Remethylation pathway} \]

\[ \text{Metabolic roles of folate and related B vitamins} \]

\[ \text{Trans-sulfuration Pathway} \]
Methylenetetrahydrofolate reductase (MTHFR)

SUBSTRATE: 5,10 methylenetetrahydrofolate

PRODUCT: 5 methyltetrahydrofolate

COFACTOR: Flavin Adenine Dinucleotide (FAD)

PRECURSOR: Riboflavin (vitamin B2)

• Polymorphic mutations in MTHFR
  – MTHFR 677C→T Polymorphism
    • C to T substitution at base pair 677
    • Alanine/valine change in the amino acid sequence
    • Functionally defective enzyme
Is this common folate polymorphism a risk factor for cardiovascular disease?

• Homozygosity (TT genotype) results in lower MTHFR enzyme activity and increased homocysteine concentrations *in vivo*

• Excess risk of CVD (by 14-21%)\(^1\)-\(^4\) in individuals with the TT genotype, but large geographical variation between countries

\(^1\)Wald DS et al. *BMJ* 2002; 325: 1202–1206.
\(^4\)Holmes et al. *Lancet* 2011; 378: 584-594
MTHFR 677TT genotype and hypertension

Meta-analysis of 20 studies; 4461 participants

- OR 1.87 (95% CI 1.31-2.68); P=0.001

Genotype-specific response to riboflavin

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<tr>
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<th>CC</th>
<th>CT</th>
<th>TT</th>
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<tr>
<td>(n = 27)</td>
<td>10.7</td>
<td>12.2</td>
<td>17.6</td>
</tr>
<tr>
<td>(n = 26)</td>
<td>10.9</td>
<td>11.8</td>
<td>13.0*</td>
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Baseline                   | 10.7 | 12.2 | 17.6 |
After intervention          | 10.9 | 11.8 | 13.0*|

Riboflavin 1.6mg/d 12 weeks

McNulty et al. 2006 Circulation 113(1), 74-80
This gene has an important role in determining blood pressure in CVD patients.
This gene-nutrient interaction has a novel role in treating hypertension in CVD patients.

Three major changes occurred:
- β-blockers omitted
- Shift from monotherapy to polytherapy
- Drug choice depended on age and race
Systolic BP response in CVD patients with the TT genotype

Results of 4-year follow-up

• The MTHFR 677TT genotype remained a risk factor for hypertension in this high-risk cohort over the 4-year period

• Riboflavin intervention resulted in an overall decrease of 9mmHg SBP and 6mmHg DBP
  • This BP-lowering effect of riboflavin occurred irrespective of current antihypertensive therapy
Role of this novel gene nutrient interaction in treating hypertension (no overt CVD)

• Blood pressure in treated hypertensive individuals with the MTHFR 677TT genotype responded significantly to riboflavin

Primary Prevention of CVD

Role of this novel gene-nutrient interaction in the prevention of hypertension?

Some unanswered questions

• What are the determinants of blood pressure in adults at all ages?
  • How important is MTHFR genotype relative to other factors?
  • And what about drugs?

• Can MTHFR genotype increase the risk of developing hypertension?
  • Does riboflavin status matter?

• The JINGO project provided the means to address these questions

Some slides showing unpublished data from the JINGO project have been removed from this presentation
Impact
Potentially affected population who can benefit?

- Gene x nutrient = phenotype

- MTHFR gene x riboflavin = blood pressure

- ‘Normalising’ the activity of the variant MTHFR enzyme by increasing riboflavin status will lower blood pressure and prevent the development of hypertension

- The **affected population** who can benefit in will be influenced by **both** the genetic factor (i.e. frequency of TT genotype) **and** riboflavin status (i.e. prevalence of deficient or low status).
Frequency of \textit{MTHFR} 677TT genotype worldwide

Low riboflavin status is a global health issue

[Unpublished data from Ulster in collaboration with UBC, Vancouver Canada]

- **NANS (n=1130)**
  - Adequate (≤1.30): 36%
  - Suboptimal (1.31-1.39): 41%
  - Deficient (≥1.40): 23%

- **TUDA (n=5192)**
  - Adequate (≤1.30): 29%
  - Suboptimal (1.31-1.39): 52%
  - Deficient (≥1.40): 19%

- **Cambodia, urban (n=146)**
  - Adequate (≤1.30): 13%
  - Suboptimal (1.31-1.39): 9%
  - Deficient (≥1.40): 78%

- **Cambodia, rural (n=156)**
  - Adequate (≤1.30): 9%
  - Suboptimal (1.31-1.39): 10%
  - Deficient (≥1.40): 81%

- **Young Canadians (n=51)**
  - Adequate (≤1.30): 37%
  - Suboptimal (1.31-1.39): 33%
  - Deficient (≥1.40): 29%

- **Elderly Canadians (n=226)**
  - Adequate (≤1.30): 25%
  - Suboptimal (1.31-1.39): 61%
  - Deficient (≥1.40): 14%
CVD mortality risk increases as BP rises

Cardiovascular Mortality Risk

Systolic/Diastolic Blood Pressure (mmHg)

115/75 135/85 155/95 175/105

2x 4x 8x

Chobanian AV et al. *JAMA* 2003;289:2560-2572
Impact of reducing BP

- Meta-analysis of 61 prospective studies including over 1 million adults\(^1\)

Each 2 mmHg decrease in SBP

10% reduction in risk of stroke mortality

Potential public health significance of this gene-nutrient interaction on BP could be very significant

\(^1\)Lewington et al. 2002 *Lancet*; **360**:1903-1913.
Impact of riboflavin intervention (personalised)
Relative to other Nutrition/Lifestyle factors to reduce BP

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Data (modified) from Chobanian et al. 2003 JNC 7 report.
*Data from 3 published trials from Ulster: Horigan et al 2010; Wilson et al 2012 & 2013
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Take-home messages

• **Individual** as well as **Population-based** approaches are needed to prevent hypertension and thus cardiovascular disease

• **A novel genetic risk factor**, present in 10% of people worldwide, increases the risk of *developing* hypertension

• **Riboflavin** (vitamin B2) can play an important role in treating and preventing hypertension *specifically* in people with the relevant genetic variant
  - Independent of current antihypertensive therapy

• **Ongoing and Future work**
  - Potential for maintaining better cardiovascular health through a *personalised approach* to preventing/treating hypertension
  - Confirmation of these results in other populations in the world
  - Hypertension in pregnancy

*TT genotype for the C677T polymorphism in the MTHFR gene*
My thanks to......All my colleagues in NICHE especially

Our Collaborators in TCD and SJH
John Scott
Anne Molloy
Conal Cunningham
Miriam Casey

The JINGO (inc TUDA and NANS) project teams at Ulster, TCD UCD, UCC

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Carol Wilson (2010)
Rosie Reilly (2014)
Emma Hughes (current)
Amy McMahon (current)

Clinical Collaborators
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