基于血游离核黄素浓度的变化探讨我国成年男性核黄素平均需要量

韦京豫
（军事医学科学院卫生学环境医学研究所　高级实验师）

中国成年男性
核黄素平均需要量
研　究

韦京豫，高蔚娜，蒲玲玲，唐振闯，
胡　南，李凌燕，陈明，赵雅倩，
郭长江，徐琪寿，顾景范
军事医学科学院

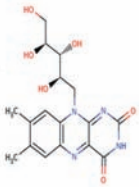
核黄素缺乏症状

每日摄入0.55mg核黄素89天或更长时间即可出现临床缺乏症状

核黄素（维生素 B_2）发　现

内脏、乳类、蛋类和一些新鲜蔬菜中富含核黄素

- 1879年，从牛乳得到粗提物（lactochrome）。
- 1933年，Kuhn，Gyorgy，Wagner从蛋清和乳汁中提取了核黄素，称之为卵黄素、乳黄素（Ovoflavin，lactoflavin），具有促进动物生长和治疗皮炎的作用。
- 1934－1935年，Kuhn's 研究小组鉴定了核黄素的结构并人工合成了核黄素。



核黄素与同型半胱氨酸

Riboflavin Lowers Homocysteine in Individuals Homozygous for the *MTHFR* 677C→T Polymorphism

Helene McNulty, PhD; Le Roy C. Dowey, PhD; J.J. Strain, PhD; Adrian Dunne, PhD; Mary Ward, PhD; Anne M. Molloy, PhD; Lindhan B. McAuena, PhD; Joan P. Hughes, MSc; Mary Hannon-Fletcher, PhD; John M. Scott, ScD

Background—Meta-analyses predict that a 25% lowering of plasma homocysteine would reduce the risk of coronary heart disease by 11% to 16% and stroke by 19% to 24%. Individuals homozygous for the methylenetetrahydrofolate reductase (*MTHFR*) 677C→T polymorphism have reduced MTHFR enzyme activity resulting from the inappropriate loss of the riboflavin cofactor, but it is unknown whether their typically high homocysteine levels are responsive to improved riboflavin status.

Methods and Results—From a register of 600 healthy adults 18 to 65 years of age of known *MTHFR* 677C→T genotype, we identified 35 with the homozygous (TT) genotype and age-matched individuals with heterozygous (CT; n=36) or wild-type (CC; n=28) genotypes to participate in an intervention in which participants were randomized by genotype group to receive 1.6 mg/d riboflavin or placebo for a 12-week period. Supplementation increased riboflavin status to the same extent in all genotype groups (8% to 12% response in erythrocyte glutathione reductase activation coefficient; $P<0.01$ in each case). However, homocysteine responded only in the TT group, with levels decreasing by as much as 22% overall (from 16.1±1.5 to 12.5±0.8 μmol/L; $P=0.003$; n=32) and markedly so (by 40%) in those with lower riboflavin status at baseline (from 22.0±2.9 and 13.2±1.0 μmol/L; $P=0.010$; n=16). No homocysteine response was observed in the CC or CT groups despite being preselected for suboptimal riboflavin status.

Conclusions—Although previously overlooked, homocysteine is highly responsive to riboflavin, specifically in individuals with the *MTHFR* 677 TT genotype. Our findings might explain why this common polymorphism carries an increased risk of coronary heart disease in Europe but not in North America, where riboflavin fortification has existed for >50 years. (Circulation. 2006;113:74-80.)

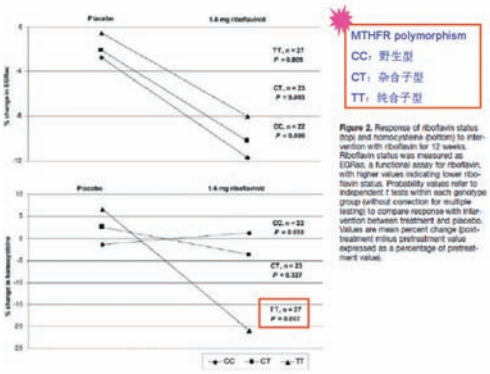
Key Words: cardiovascular diseases ■ homocysteine ■ methylenetetrahydrofolate reductase (NADPH2) ■ nutrition ■ riboflavin

核黄素的主要作用

- FAD，FMN参与呼吸链的电子传递
- FAD 参与丙酮酸和 α－酮戊二酸的脱羧反应
- FAD 作为脂酰辅酶A脱氢酶的辅酶参与脂肪酸氧化
- FAD 参与吡哆醛转化为吡哆酸的过程
- FMN参与磷酸吡哆醛的形成
- FAD参与视黄醛转化为视黄酸的过程
- FAD参与5－甲基叶酸的合成
- FAD参与色氨酸转化为尼克酸的过程
- FAD 参与GSSG转化为GSH的过程
- FAD与细胞色素P450结合，参加药物代谢

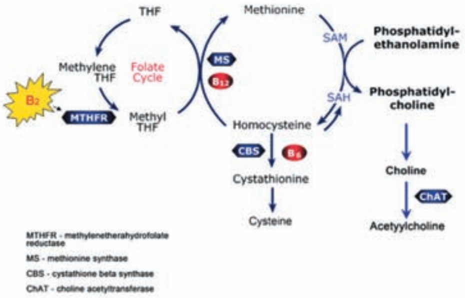
F↹FMN↹FAD

核黄素在体内以FAD和FMN发挥作用



MTHFR polymorphism
CC：野生型
CT：杂合子型
TT：纯合子型

Figure 2. Response of riboflavin status (top) and homocysteine (bottom) to intervention with riboflavin for 12 weeks. Riboflavin status was measured as EGRac, a functional assay for riboflavin, with higher values indicating lower riboflavin status. Probability values refer to independent *t* tests within each genotype group (without correction for multiple testing) to compare response with intervention between treatment and placebo. Values are mean percent change (post-treatment minus pretreatment value expressed as a percentage of pretreatment value).



核黄素与高血压

Riboflavin lowers blood pressure in cardiovascular disease patients homozygous for the 677C—T polymorphism in *MTHFR*

Geraldine Horigan[a], Helene McNulty[a], Mary Ward[a], J.J. Strain[a], John Purvis[b] and John M. Scott[c]

Objective The purpose was to examine the effect of intervention with riboflavin (a cofactor for MTHFR) on blood pressure in patients homozygous (TT genotype) for the common 677C—T polymorphism in MTHFR.

Methods We investigated 197 premature cardiovascular disease patients, prescreened for the *MTHFR* 677C—T polymorphism, from an original cohort of 404 to select those with the TT genotype (n = 60) and a similar number with heterozygous (CT; n = 65) or wild-type (CC; n = 75) genotypes. Of these, 181 completed an intervention in which participants were randomized within each genotype group to receive 1.6 mg per day riboflavin or placebo for 16 weeks.

Results Among patients taking one or more antihypertensive drugs at recruitment (82%), we observed that target blood pressure (<140/90 mmHg) had been achieved in only 37% patients with the TT genotype compared with 59% with the CT and 64% with the CC genotype (P<0.001). Riboflavin intervention reduced mean blood pressure specifically in those with the TT genotype (from 144/87 to 131/80 mmHg; P<0.05 systolic; P<0.05 diastolic), with no response observed in the other genotype groups.

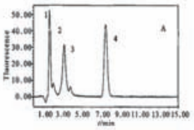
Conclusion Riboflavin is effective in reducing blood pressure specifically in patients with the MTHFR 677 TT genotype. The findings, if confirmed, may have important implications for the prevention and treatment of hypertension. *J Hypertens* 28:478–486 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

核黄素营养状况的评价

- 膳食摄入量
- 缺乏症状
- 空腹尿、任意尿排出量
- 4h尿负荷试验（正常>800mg）
- 谷胱甘肽还原酶活性系数（红细胞或全血）（AC正常<1.2，缺乏>1.4）
- 红细胞含量
- ★ 血清含量

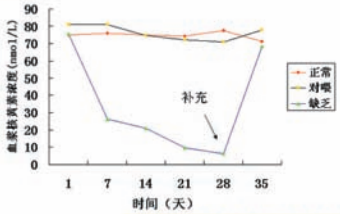
核黄素营养状况评价方法及其标准需要重新研究

核黄素缺乏后大鼠血清核黄素含量动态变化



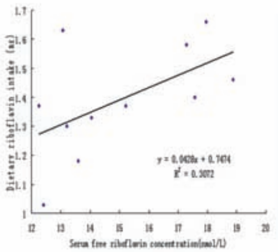
FMN、FAD也有类似变化，但是不稳定。

核黄素尿排量与BGRAC变化幅度相对较小。



徐琪寿等，营养学报 2005，27：386

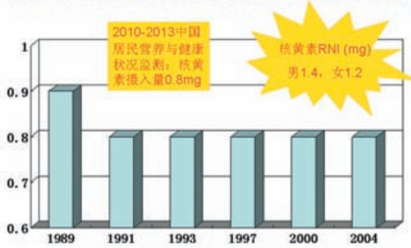
我国成年男性血清核黄素正常水平的研究



将中国营养学会推荐的成年男性膳食核黄素RNI（1.4mg）代入相关公式，计算得血清游离核黄素浓度为15.3nmol/L，如减去1.96个标准差，则得下限值10.4 nmol/L，此值与上述通过4h尿负荷核黄素排出量推算出来的正常人员血清游离核黄素浓度下限值接近。

郭长江等，营养学报 2008,30:542

我国居民膳食核黄素摄入量的变化



1989～2004我国居民人均膳食核黄素摄入量的变化分析

翟凤英等，2008

Qestioning riboflavin recommendations on the basis of a survey in China

T Colin Campbell, Thierry Brun, Chen Junshi, Feng Zulin, BanooParpia

Am J Clin Nutr 1990,51:436-45

Conclusion:

......Approximately 90% of the survey subjects were found to be deficient by Western and Chinese reference standards and allowances. Upon reconsideration of the Western experimental data originally used to establish these recommendations, it is suggested that riboflavin allowances are set too high both in China and in Western countries.

目前我国核黄素RNI是根据尿负荷试验结果制订的。我国居民核黄素营养状况可能处于"亚健康"状态。

中国成年男性核黄素需要量研究

王成发等

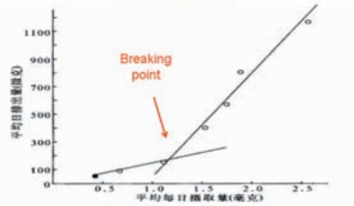


图 2 核黄素摄入量（mg）与全日尿排出量（μg）的关系

营养学报，2006

我国成年男性膳食核黄素推荐摄入量调查研究

- 调查南北方11个集中供膳单位膳食核黄素摄入量1.0－1.7mg。
- 能量消耗在14.9－16.9MJ（3566.9－4147.3 kcal），基本上处于重度劳动强度范围。
- 4h尿负荷试验核黄素营养状况处于正常状态人员较少（0－28.6%），处于缺乏或不足状态的人员较多。
- 将尿负荷试验结果中核黄素缺乏人员比例低于10%以内的4个单位核黄素摄入量进行统计分析，得平均值为1.5mg。

郭长江等，解放军预防医学杂志 2010

我国成年男性膳食核黄素推荐摄入量干预研究

一组：基础膳食+0.0mg
二组：基础膳食+0.2mg
三组：基础膳食+0.4mg
四组：基础膳食+0.6mg
五组：基础膳食+0.8mg
六组：基础膳食+1.0mg

化学分析法：基础膳食核黄素含量1.0mg
称重调查法：基础膳食核黄素含量1.2mg
双份饭
生活观察
共78人
时间 6 周

血清核黄素含量
空腹尿核黄素含量
尿负荷试验
全血谷胱甘肽还原酶
活性系数
能量消耗

“战前”动员

Table 1 Characteristics of study subjects in different groups

Group	n	Age (year)	Height (cm)	Body weight (kg)	BMI
1	13	21±2	175.2±3.9	62.9±6.5	20.5±1.6
2	13	20±1	174.8±7.0	68.8±13.8	22.5±3.1
3	13	20±2	174.9±5.9	67.5±6.4	22.1±1.9
4	13	21±2	170.0±5.2	66.1±6.0	22.9±1.4
5	13	21±2	176.8±6.1	67.9±8.7	22.0±2.8
6	13	20±1	172.5±5.8	65.4±5.8	22.0±2.4

Table 2 Energy expenditure of the study subjects

Groups	n	kcal/d
1	4	3796.6±746.1
2	4	3830.1±297.3
3	3	3740.6±523.3
4	3	3419.5±323.5
5	3	3477.0±674.4
6	3	3737.2±520.4

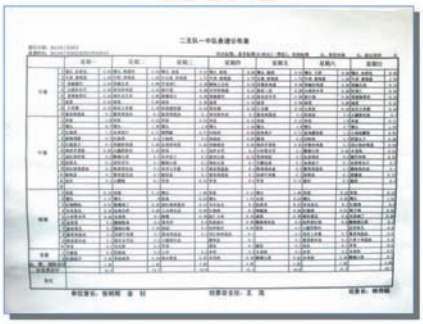
核黄素“饮料”

Table 3 Riboflavin supplementation in different groups

Groups	n	Dose (mg/d)
1	13	0
2	13	0.2
3	13	0.4
4	13	0.6
5	13	0.8
6	13	1.0

膳食调查
称重法

一周食谱

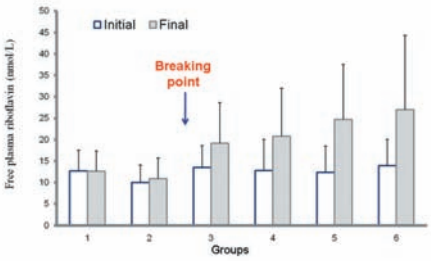


采 血

Table 4 Results of dietary survey

Energy and nutrients	Daily intakes
Energy (kcal)	3316.7±153.6
Protein (g)	89.6±10.1
Calcium (mg)	615.7±62.8
Phosphorus (mg)	1139.5±68.1
Iron (mg)	43.2±1.1
Zinc (mg)	13.2±1.0
Selenium (μg)	53.7±8.4
Vitamin A (μgRE)	801.3±90.4
Vitamin E (mg)	25.5±4.8
Thiamine (mg)	1.3±0.2
Riboflavin (mg)	1.2±0.2
Niacin (mg)	18.2±8.5
Vitamin C (mg)	127.9±32.4

游离血核黄素水平



“双份饭”
收集与处理

游离血核黄素水平双曲线拟合

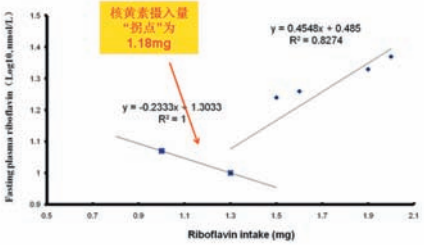


Table 5 Dietary riboflavin intake based chemical analysis

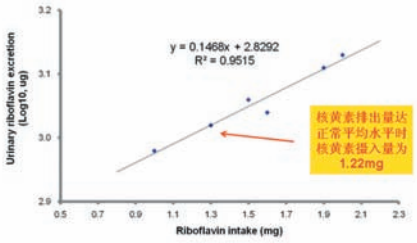
Groups	n	Intake (mg/d)
1	16	1.0±0.2
2	17	1.1±0.3
3	15	1.1±0.3
4	16	1.0±0.2
5	16	1.1±0.3
6	15	1.0±0.2

Table 6 Results of BGRAC analysis

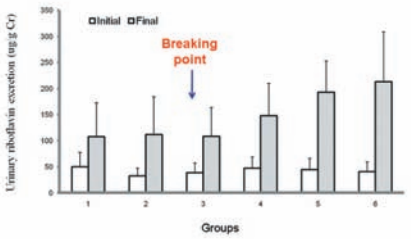
Groups	Initial	Final
1	1.11±0.07	1.11±0.06
2	1.21±0.15	1.16±0.05
3	1.07±0.04	1.11±0.06
4	1.08±0.06	1.08±0.05
5	1.23±0.18	1.03±0.09
6	1.20±0.13	1.07±0.08

收　尿

尿核黄素负荷试验



空腹尿核黄素含量



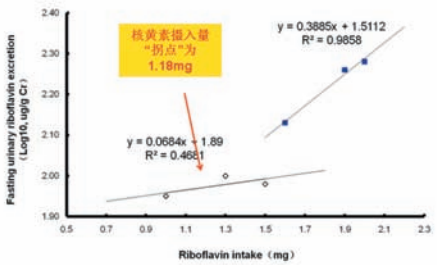
结　论

- 游离血核黄素水平变化，核黄素摄入量“拐点”为1.18mg
- 根据空腹尿核黄素含量变化，核黄素摄入量“拐点”为1.18mg
- 根据尿负荷试验结果，核黄素排出量达正常水平时核黄素摄入量为1.22mg

→ 中国成年男性
核黄素EAR
1.20mg
核黄素RNI
1.44mg

？
烹调损失
16%
能量消耗

空腹尿核黄素含量双曲线拟合



谢　谢

达能营养中心
所有参加工作的志愿者