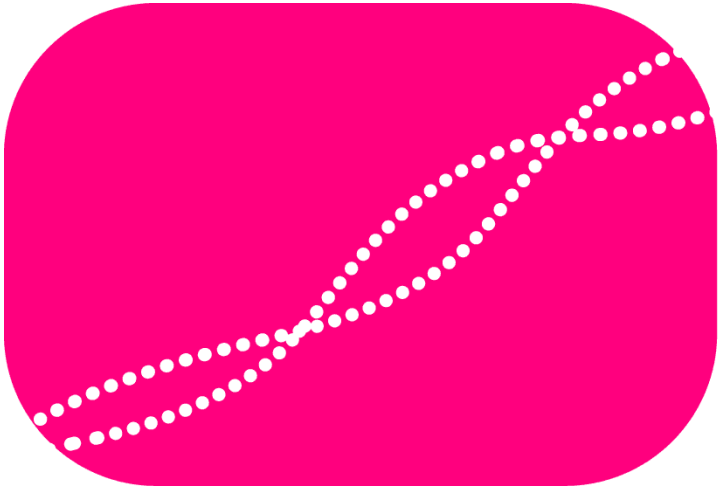
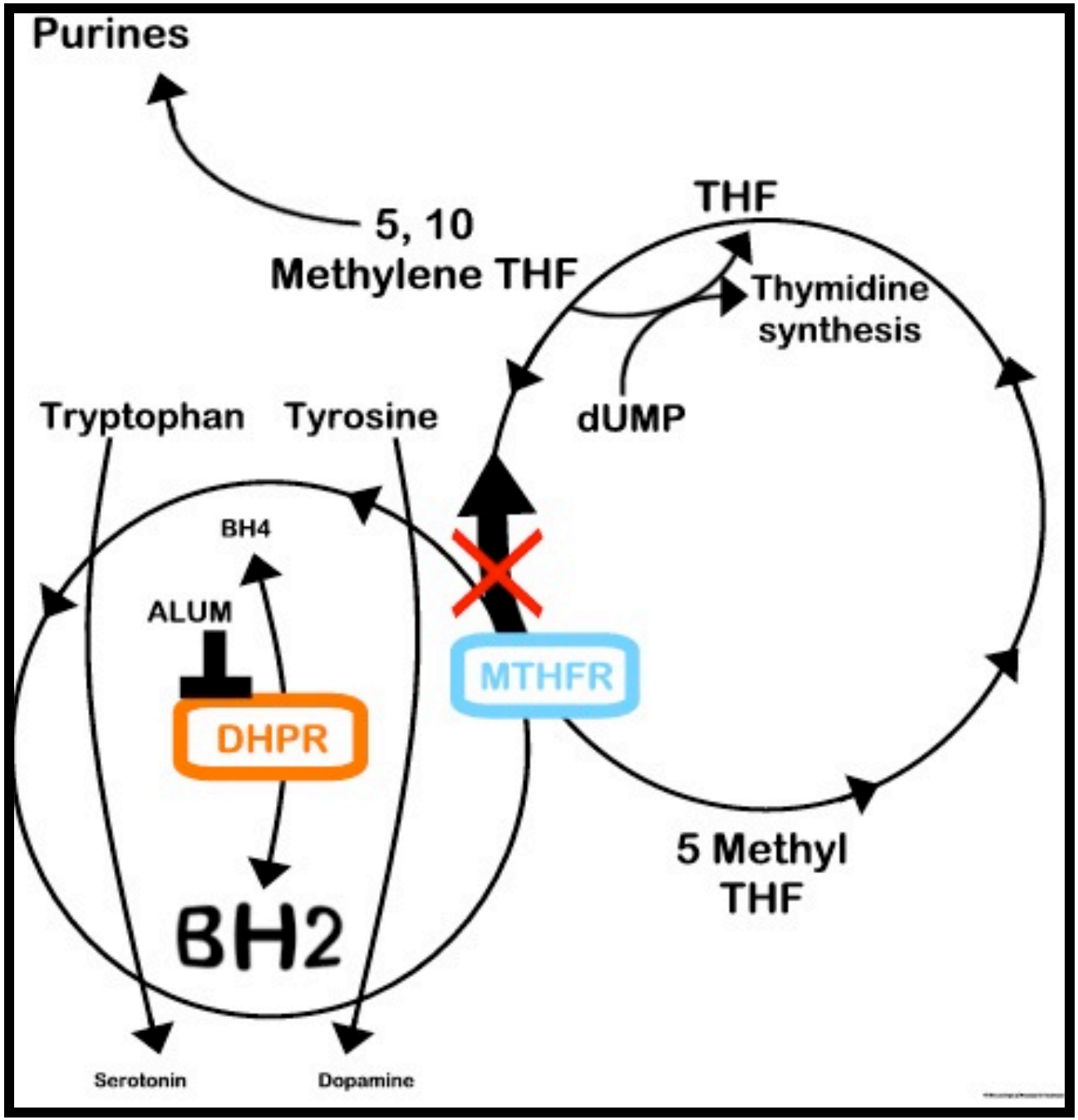
MTHFR A1298C




Purines
5, 10
Methylene THF
THF
Thymidine
synthesis
dUMP
Tryptophan
Tyrosine
BH4
ALUM
DHPR
MTHFR
5 Methyl
THF
BH2
Serotonin
Dopamine

A1298C

MTHFR

A1298C

American Journal of
EPIDEMIOLOGY

Volume 157
Number 7
April 1, 2003

Sponsored by the Society for Epidemiologic Research
Published by Oxford University Press

HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEW

5,10-Methylenetetrahydrofolate Reductase Polymorphisms and Leukemia Risk: A HuGE Minireview

Kim Robien[1,2] and Cornelia M. Ulrich[1,2,3]

A1298C polymorphism

A second *MTHFR* polymorphism, *A1298C* in exon 7, results in a glutamate-to-alanine substitution at codon 429 (5, 13). This polymorphism lies in the *S*-adenosylmethionine-regulatory domain of the enzyme (17–19). The binding of *S*-adenosylmethionine (SAM) results in conformational changes within the MTHFR enzyme that inhibit the enzyme's activity (17). Lymphocytes from individuals with the *1298 CC* genotype have been found to have approximately 60 percent specific wild-type in vitro MTHFR activity (13), and individuals with both *677 CT* and *1298 AC*

MTHFR

A1298C

A1298C allele

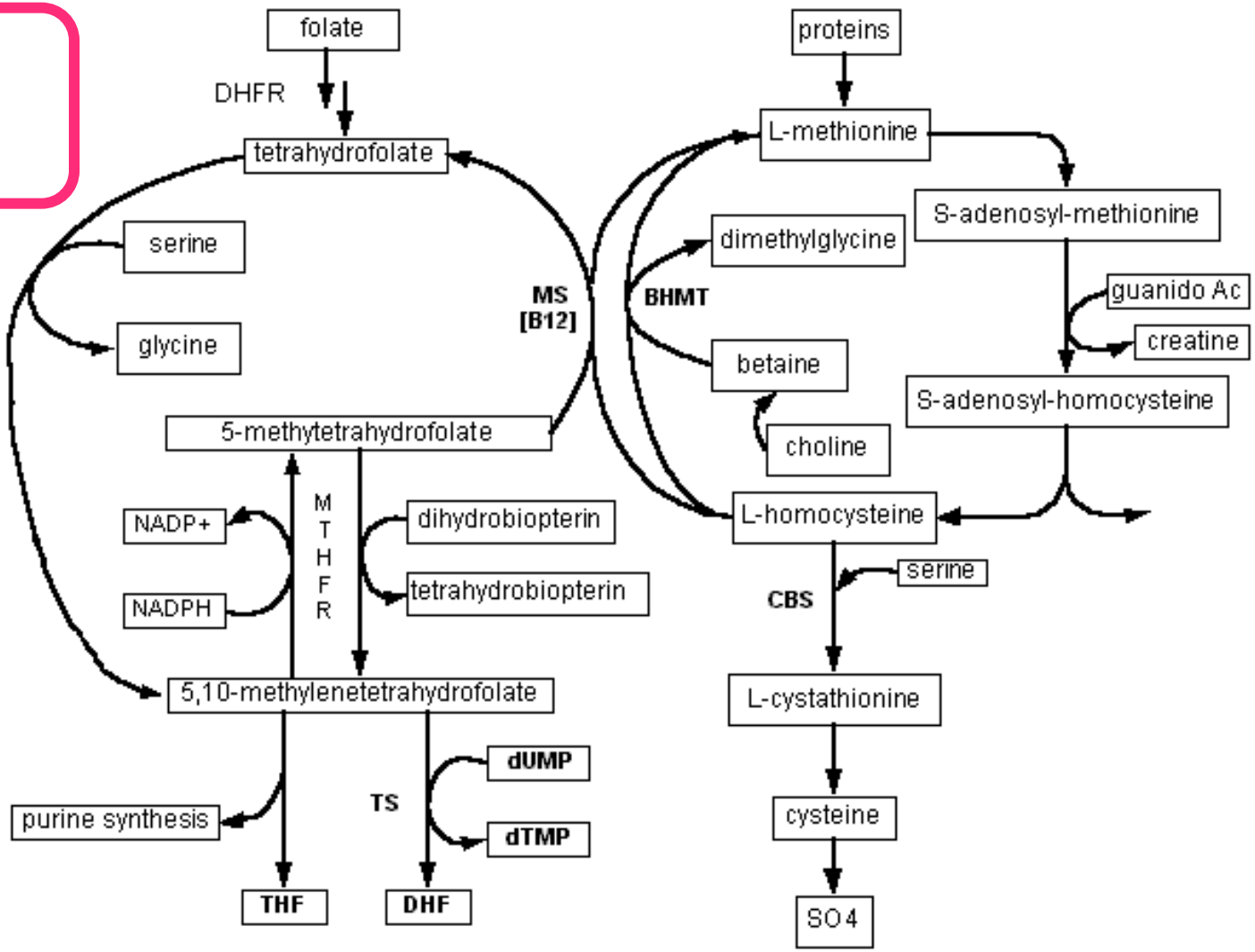
To date, data on the prevalence of the **A1298C** allele in the population is limited to relatively small groups of controls from case-control studies. The frequency of **A1298C** homozygotes among controls was approximately 9 percent in two studies, one from Canada (11) and one from the Netherlands (12). Still among controls, the frequency of C677T/**A1298C** compound heterozygotes was 15 percent in the Canadian study (11) (18 percent in the mothers and 11 percent in the children), 20 percent in the Dutch study (12), and appeared to be 17 percent in a U.S. study (13).

MTHFR gene and congenital anomalies Am J Epidemiol 2000 May 1;151(9):862-877

5, 10-Methylenetetrahydrofolate reductase (***MTHFR***) Gene Variants and Congenital Anomalies
Lorenzo D. Botto and Quanhe Yang

MTHFR

A1298C



This chart depicts the metabolic roles of the monocarbon folate pool, and its relationship to methionine metabolism. 5,10-methylenetetrahydrofolate - produced when serine donates a carbon to tetrahydrofolate - provides carbon groups for synthesis of purines as well as deoxythymidine monophosphate (dTMP) - crucial for DNA synthesis and repair. (10-formyl tetrahydrofolate also participates in purine synthesis - not depicted here.)

Nutritional Supplementation and Down's Syndrome - Focus on Folate Mark F. McCarty

Methylenetetrahydrofolate Reductase

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 259, No. 19, Issue of October 10, pp. 11647-11650, 1984
Printed in U.S.A.

EVIDENCE FOR SPATIALLY DISTINCT SUBUNIT DOMAINS OBTAINED BY SCANNING TRANSMISSION ELECTRON MICROSCOPY AND LIMITED PROTEOLYSIS*

(Received for publication, May 21, 1984)

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Regulation of the forward MTHFR reaction by SAMe

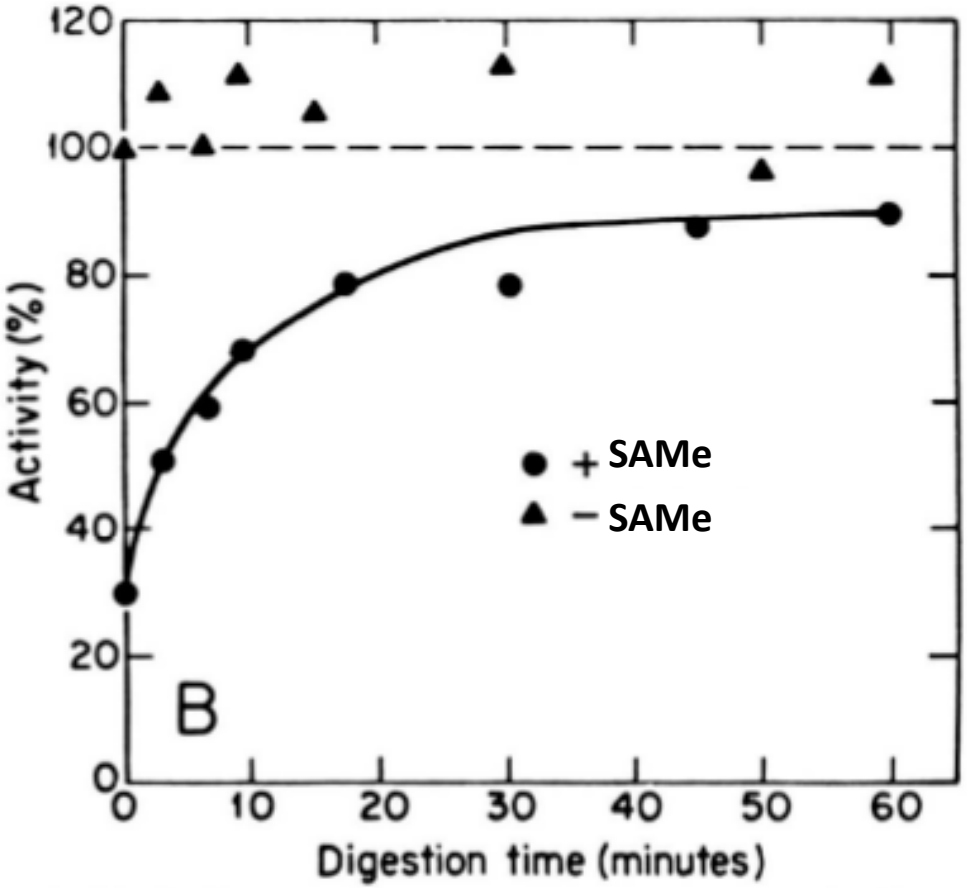

FIG. 3. **Limited proteolysis of methylenetetrahydrofolate reductase**

J. ment. Defic. Res. (1982) 26, 21–25

TETRAHYDROFOLATE AND HYDROXOCOBOLAMIN IN THE MANAGEMENT OF DIHYDROPTERIDINE REDUCTASE DEFICIENCY

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INTRODUCTION

The clinical importance of the maintenance of the correct levels of cellular tetrahydrobiopterin has been shown from malignant hyperphenylalaninaemia, variant forms of phenylketonuria which have a deficiency in tetrahydrobiopterin metabolism (Danks *et al.*, 1978; Leeming, Pheasant & Blair, 1981). Manipulation of the level of tetrahydrobiopterin within the cell could be of use in the therapy and management of malignant hyperphenylalaninaemia and other neurological illnesses. The purpose of this paper is to describe one of these possibilities.

MATERIALS AND METHODS

Reduced nictotinamide adenine dinucleotide phosphate (NADPH) and Tris were obtained from Sigma Chemical Company, ascorbate and hydroxocobalamin from British Drug Houses Limited and 5-methyltetrahydrofolate, magnesium salt from Eprova.

Fresh rat brain was homogenized at 0–4°C in three volumes of 0.01 M Tris/HCl, 0.04 M KCl buffer adjusted to pH 8.0. The homogenate was centrifuged at 19 000 *g* for 1 hour at 0°C and the supernatant used in the assay. The *in-vitro* synthesis of biopterin derivatives and the effects of 5-methyltetrahydrofolate, hydroxocobalamin and ascorbate on the synthesis were determined in the following manner in triplicate: 0.6 ml 0.083 M Tris/HCl buffer pH 8.0 was added to 0.2 ml of distilled water (controls) or 0.2 ml of

* Address correspondence to R. J. Leeming.
Received 12 October 1981
0022–264X/82/0300–0021$02.00

5 methyl THF increases BH4 levels

additive followed by 0.05 ml 20 m.mol/ml reduced nicotinamide adenine dinucleotide (NADPH), 0.05 ml 60 m m.mol/ml guanosine triphosphate and finally 0.1 ml of brain supernatant. Incubation was carried out in the dark at 37°C in a shaking water bath for three hours. 2.0 ml 0.1 M HCl was added and dilutions were made in 0.2 M phosphate buffer pH 5.0 for assay with Crithidia fasciculata (Leeming *et al.*, 1976). The protein content of the brain extract was measured by the biuret method (Layne, 1957).

The response to treatment of dihydropteridine reductase deficiency in a previously reported case (D.P.) (Rey *et al.*, 1977) was examined further.

RESULTS

Controls for *in-vitro* synthesis uniformly produced 2.0–3.0 ng Crithidia active biopterin derivatives for each mg protein in the brain extract.

Ascorbate increased the synthesis (Table 1). Hydroxocobalamin and 5-methyltetrahydrofolate separately did not increase the synthesis nor did hydroxocobalamin add significantly to the rise created by ascorbate while 5-methyltetrahydrofolate did ($P<0.001$) (Table 1). However ascorbate, hydroxocobalamin and 5-methyltetrahydrofolate gave the maximum increase ($P<0.001$) (Table 1).

Table 1. The effects of ascorbate, 5-methyltetrahydrofolate and hydroxocobalamin on the in-vitro synthesis of biopterin

	No. of assays	*Percentage of control*	*Significance of increase compared to control by Student's t test*
Ascorbate			
2.8×10^{-1} M	6	150	$P<0.002$
2.8×10^{-2} M	6	132	$P<0.0025$
2.8×10^{-3} M	12	107	$P<0.005$
5-methyltetrahydrofolate			
1.1×10^{-4} M	6	102	n.s.
1.1×10^{-4} M plus 2.8×10^{-1} M ascorbate	12	165	$P<0.001$
Hydroxocobalamin			
1.1×10^{-7} M	6	97	n.s.
1.1×10^{-7} M plus 2.8×10^{-1} M ascorbate	6	150	$P<0.001$
1.1×10^{-4} M 5-methyltetrahydrofolate plus 1.1×10^{-7} M hydroxocobalamin plus 2.8×10^{-1} M ascorbate	6	207	$P<0.001$

DISCUSSION

Malignant hyperphenylalaninaemia is found in about 1% of cases of phenylketonuria. It may be a model for the understanding and therapy of other neurological disorders

J. ment. Defic. Res. (1986) 30, 179–183

THE EFFECT OF TETRAHYDROFOLATE ON TETRAHYDROBIOPTERIN METABOLISM

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INTRODUCTION

The co-factor essential for the hydroxylation of tyrosine and tryptophan, and, therefore, necessary for the biosynthesis of the monoamine neurotransmitters, is 5,6,7,8-tetrahydrobiopterin (BH_4) (Leeming, Pheasant & Blair, 1981). BH_4 levels are maintained *in vivo* by a *de novo* pathway from guanosine triphosphate and salvage from the inactive quinonoid dihydrobiopterin by dihydropteridine reductase (Figure 1). Disruption of either path can have a serious effect on the brain BH_4 level. Deficiency of BH_4 in the brain is known to cause severe mental defects (Leeming, Pheasant & Blair, 1981). The levels of BH_4 in the cerebrospinal fluid of subjects dying with senile dementia of the Alzheimer type (SDAT) have been found to be reduced (Morar *et al.*, 1983) and the biosynthesis of BH_4 has been found to be grossly impaired which suggests that a defect of BH_4 metabolism could be involved in this condition, (Barford *et al.*, 1984).

The role of folate and vitamin B_{12} in the biosynthesis of BH_4 is unknown, but both have been found to enhance its biosynthesis in rats (Leeming *et al.*, 1982). In senile dementia of the Alzheimer type (SDAT), the level of red cell folate has been found to be significantly lower than controls (Sneath *et al.*, 1973) and folate deficiency has been associated with dementia (Reynolds, 1976). Vitamin B_{12} deficiency has been reported to be associated with neuropathy, dementia (Walton, 1977) and mental retardation in infants (Hoey *et al.*, 1982). The vitamin B_{12}-catalysed 5-methyltetrahydrofolate transferase reaction is inhibited by nitrous oxide by the oxidation of the active reduced cobalt I centre (Banks, Henderson & Pratt 1968; Perry *et al.*, 1983). Prolonged nitrous oxide exposure in man has been found to cause neurological disorder (Layzer, 1978; Amess *et al.*, 1978). The apparent involvement of folate and vitamin B_{12} in neurological disease led us to investigate their role in BH_4 biosynthesis in human and rat brain tissue.

MATERIALS AND METHODS

Reduced nicotinamide adenine dinucleotide phosphate (NADPH), guanosine triphosphate (GTP), ascorbate and Tris were obtained from Sigma Chemical Company,

Received 28 January 1985; revised 22 September 1985

5 methyl THF increases BH4 levels

RESULTS AND DISCUSSION

BH_4 biosynthesis in rat brains is significantly increased by the addition of 5-methyltetrahydrofolate ($P<0.01$) (Table 1), a finding similar to that found by Leeming *et al.* (1982). In normal human temporal lobe there is no significant increase. In patients dying with SDAT, BH_4 biosynthesis has been found to be impaired (Table 1), as previously reported (Barford *et al.*, 1984). In SDAT brain synthesis can be enhanced into the normal range by the addition of 5-methyltetrahydrofolate ($P<0.05$). Thus, reduced folate levels in dements (Sneath *et al.*, 1983) may cause impaired BH_4 biosynthesis.

Further evidence for the possible involvement of folate in BH_4 metabolism comes from studies on postmortem brain from a child with methylene tetrahydrofolate reductase deficiency, a condition in which the conversion of methylenetetrahydrofolate to 5-methyltetrahydrofolate does not occur (Erbe, 1979). In this brain, BH_4 biosynthesis was zero and the addition of 5-methyltetrahydrofolate to the incubate resulted in BH_4 synthesis (LC, Table 1). In this subject the effect of orally administered 5-methyltetrahydrofolate had been apparent in life for it was found to cause a transient rise in CSF biopterin (Clayton *et al.*, 1986).

Tetrahydrofolate was also found to result in clinical improvement in a child with reduced BH_4 levels due to dihydropteridine reductase deficiency (Leeming *et al.*, 1982; Harpey, Rey & Leeming, 1985).

When *in vitro* synthesis of BH_4 was examined in postmortem infant brain samples in the absence of 5-methyltetrahydrofolate under a nitrous oxide atmosphere the formation of BH_4 fell to zero; this was possibly due to inactivation of vitamin B_{12} by oxidation of the cobalt centre (Banks, Henderson & Pratt, 1968; Perry *et al.*, 1983). Thus, in pernicious anaemia, where vitamin B_{12} is deficient, the patients have significantly low serum biopterin levels, and this could be due to reduced BH_4 synthesis through B_{12} deficiency (Leeming *et al.*, 1976).

The results suggest that both tetrahydrofolate and vitamin B_{12} may be required for the biosynthesis of BH_4, and that the deficiency of one or the other could have a significant effect of BH_4 metabolism and thus on the neurological well-being.

Table 1. Synthesis of BH_4 in human and rat brain samples. Results are expressed as a mean ±standard deviation ng BH_4 synthesised/mg protein/h. (number of subjects in brackets)

Subject	*BH_4 biosynthesis in the absence of 5MeTHF*	*BH_4 biosynthesis in the presence of 5MeTHF*
Adult human brain samples		
Control (44–87 years)	0.66±0.48 (8)	0.76±0.44 (3)
SDAT (71–79 years)	0.07±0.12 (17)	0.40±0.25 (5)
Infant human brain samples		
Control (6 weeks–7 months)	0.31±0.11 (6)	0.41±0.05 (3)
LC (3 years)	0.00 (1)	0.62 (1)
Rat brain samples	0.88±0.37 (5)	3.7±1.0 (5)

MTHFR

A1298C

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 255, No. 13, Issue of July 10, pp. 6014-6017, 1980
Printed in U.S.A.

Characterization of the Dihydropterin Reductase Activity of Pig Liver Methylenetetrahydrofolate Reductase*

(Received for publication, March 20, 1980)

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Pig liver methylenetetrahydrofolate reductase catalyzes the reduction of quinonoid dihydropterins *in vitro*. Either NADPH or methyltetrahydrofolate can serve as the electron donor. Methylenetetrahydrofolate reductase can also support phenylalanine hydroxylation *in vitro* by regeneration of the tetrahydropterin cofactor. These results lend support to the proposal that reduction of methylenetetrahydrofolate proceeds by tautomerization of the 5-iminium cation to form quinonoid 5-methyldihydrofolate, which is then reduced to methyltetrahydrofolate (Matthews, R. G., and Haywood, B. J. (1979) *Biochemistry 18*, 4845-4851). Under V_{max} conditions, the turnover numbers for the NADPH-linked reductions of the quinonoid forms of 6,7-dimethyldihydropterin, dihydrobiopterin, and dihydrofolate are all about the same as that for the reduction of methylenetetrahydrofolate. The K_m values for racemic mixtures of the same quinonoid acceptors are 40, 30, and 20 μM, respectively, while the K_m for (6*R*,*S*)methylenetetrahydrofolate is 20 μM at pH 7.2 in phosphate buffer. The reduction of quinonoid dihydropterins is inhibited by adenosylmethionine and dihydropteroylhexaglutamate, which are known to modulate methylenetetrahydrofolate reductase activity.

MTHFR

A1298C

5-Methyltetrahydrofolate and tetrahydrobiopterin can modulate electrotonically mediated endothelium-dependent vascular relaxation

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Edited by Louis J. Ignarro, University of California School of Medicine, Los Angeles, CA, and approved March 21, 2005 (received for review December 1, 2004)

Psychological Medicine, 1992, 22, 871-876. Copyright © 1992 Cambridge University Press
Printed in Great Britain

Folate deficiency, biopterin and monoamine metabolism in depression

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SYNOPSIS Seven (21 %) of 34 patients with a severe DSM-III diagnosis of major depression had red-cell folate levels below 150 ng/ml. This subgroup with folate deficiency had significantly lower CSF 5-hydroxyindoleacetic acid (5HIAA) compared to neurological controls. For all depressed patients red-cell folate was significantly correlated with CSF 5HIAA and homovanillic acid (HVA). CSF tetrahydrobiopterin (BH_4) was significantly correlated with CSF 5HIAA and HVA and red-cell folate. Our observations provide further evidence of the links between folate, biopterin and monoamine metabolism in depression.

INTRODUCTION

There is much evidence linking depression and folate deficiency. Among the neuropsychiatric complications of megaloblastic anaemia due to folate deficiency, depression is the most common finding (Shorvon *et al.* 1980). Several studies of psychiatric in-patients have revealed that up to one-third have low serum folate levels, with a particular association with depression (Carney, 1967; Reynolds *et al.* 1970; Reynolds, 1976). As serum folate concentrations fluctuate rapidly in relation to recent dietary changes a red-cell folate assay more accurately reflects the folate status of an individual (Chanarin, 1979). Two studies of red-cell folate in psychiatric patients confirm that up to one-third may have borderline or definite folate deficiency, especially depressed patients (Reynolds *et al.* 1971; Carney *et al.* 1990). Although much of this folate deficiency may be secondary to the mental disorder for dietary reasons, open and double-blind placebo controlled trials suggest that folic acid treatment may enhance clinical response, with a particular effect on mood (Reynolds, 1967; Carney & Sheffield, 1970; Botez *et al.* 1979*a*; Coppen *et al.* 1986; Godfrey *et al.* 1990).

For many years research into neurochemical mechanisms in depression has focused on neurotransmitter metabolism, especially monoamines (Van-Pragg, 1982). It is, therefore, of interest that studies in neuropsychiatric patients (Botez *et al.* 1982), children with inborn errors of folate metabolism (Clayton *et al.* 1986; Hyland *et al.* 1988) and in experimental animals (Botez *et al.* 1979*b*) have all shown a relationship between folate and serotonin (5HT) metabolism. The mechanism of the influence of folate on 5HT metabolism is unknown, but one possibility is through an effect on tetrahydrobiopterin (BH_4) metabolism (Reynolds *et al.* 1970; Kaufman, 1991). BH_4 is an essential co-factor for tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of 5HT, and also for tyrosine hydroxylase in the synthesis of dopamine (Kaufman, 1981) (Fig. 1). A deficiency of this coenzyme has also been implicated in some patients with depression (Blair *et al.* 1984; Fleischhacker *et al.* 1985; Woggen *et al.* 1985).

We have, therefore, undertaken a study of the relationship between folate and monoamine metabolism in severely depressed patients, in some of whom we also had the opportunity to examine cerebrospinal fluid BH_4.

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Reverse reaction of MTHFR to drive BH4 synthesis

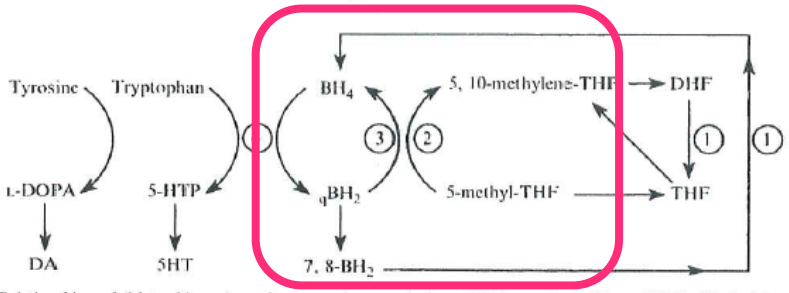


FIG 1. Relationships of folate, biopterin and monoamine metabolism. (THF, tetrahydrofolate; DHF, dihydrofolate; BH_4, tetrahydrobiopterin; qBH_2, quinoid dihydrobiopterin; 5HTP, 5-hydroxytryptophan; DA, dopamine; 5HT, serotonin; (1) dihydrofolate reductase; (2) 5,10-methylene tetrahydrofolate reductase; (3) dihydropteridine reductase; (4) tyrosine hydroxylase and tryptophan hydroxylase.)

METHOD

Patients

Blood and cerebrospinal fluid (CSF) were obtained from 34 in-patients with a DSM-III diagnosis of depression and a Hamilton rating score greater than 20; and from 10 neurological control patients (5 with unexplained peripheral neuropathy, 3 with motor neurone disease, 1 with narcolepsy and 1 with encephalomyelitis). Depressed patients with evidence of organic brain disease, severe physical illness, drug or alcohol abuse were excluded. The depressed patients included 11 males and 23 females, and had a mean age of 51·6±16·8 (range 23–74) years; the neurological controls comprised 5 males and 5 females aged 51·3±17·0 (range 25–73) years.

Procedure

All medication was withdrawn for at least one week prior to sampling. All lumbar punctures were performed between 09.00 and 11.00 hours in the recumbent position after overnight fasting. A 5 ml sample of CSF was collected into plain sterile tubes for the analysis of folate and monoamine metabolites. In 10 patients with depression 1 ml was transferred into a tube containing 1 mg/ml each of dithioerythritol (DTE) and diethylenetriamine-pentaacetic acid (DETAPAC) for the analysis of BH_4. All CSF samples were then frozen on dry ice and stored at −70 °C. On the same morning that CSF was obtained blood was withdrawn into EDTA tubes for the analysis of red-cell folate.

Approval for performing lumbar punctures with patient consent was obtained from the hospital ethical committees.

Biochemical analysis

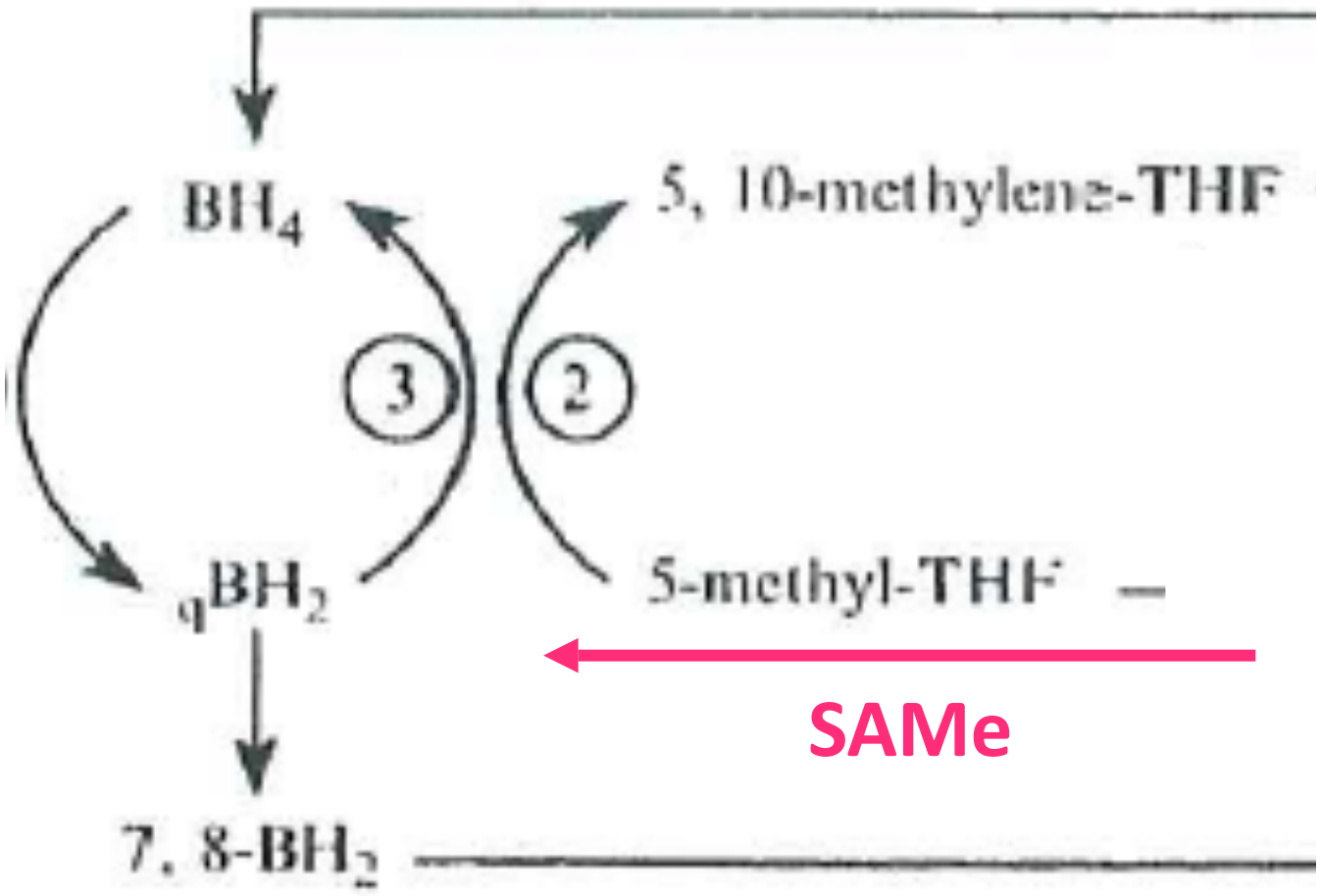
CSF 3-methoxy-4-hydroxyphenyl glycol (MHPG), 5-hydroxyindoleacetic acid (5HIAA), homovanillic acid (HVA) and BH_4 were determined by HPLC with electrochemical detection (Bottiglieri *et al.* 1984; Hyland & Howells, 1989). CSF and red-cell folate were determined by microbiological assay using *Lactobacillus casei* (Chanarin, 1989).

Statistical analysis

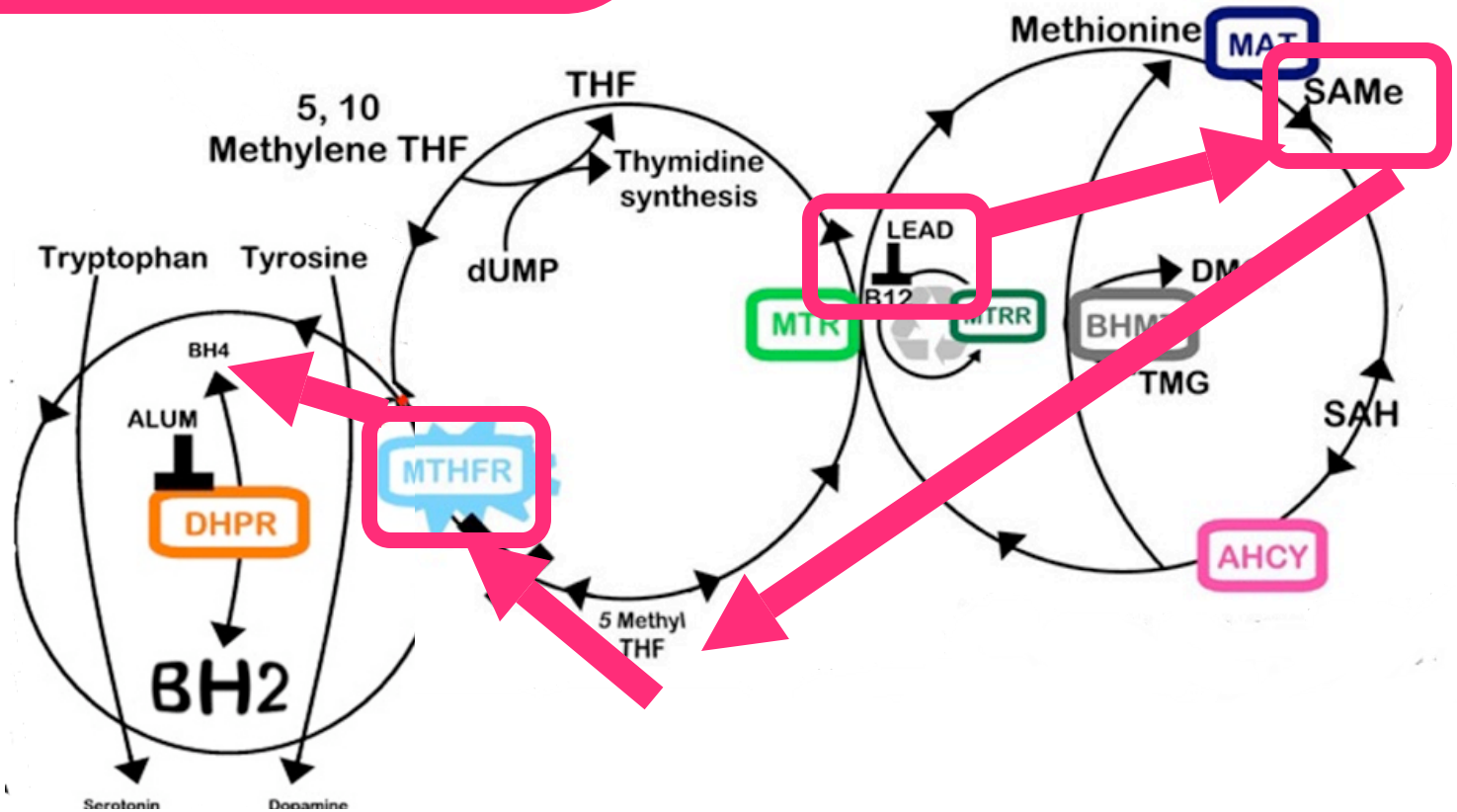
Statistical significance between groups was assessed using the pooled estimate of the standard deviation obtained by analysis of variance of log-transformed data. The t values were adjusted for multiple comparisons using Dunnett's test. Correlations were performed using the Pearson correlation coefficient.

RESULTS

Red-cell folate, CSF folate and CSF monoamine metabolite levels in control and depressed patients are summarized in Table 1. The normal reference range for red-cell folate in our laboratory is 150–550 (mean 330) ng/ml. Among the 34 depressed patients 7 (21%) had red-cell folate values below 150 ng/ml indicating severe folate deficiency. The depressed patients were, therefore, examined as a whole as well as in two subgroups of 27 with 'normal' folate and 7 with folate deficiency.


BH4
5, 10-methylene-THF
3
2
qBH2
5-methyl-THF
SAMe
7, 8-BH2

Taken together,
B12 can increase SAMe, or SAMe itself in high doses will bind to MTHFR and allow for the reverse reaction to increase BH4



Nutrigenomic Test Results

Complete Basic SNP Panel I
Characterized SNPs

Gene Name	Variation	Result	Call
ACE	Del16	+/+	DELETION
CBS	A360A	+/+	T
CBS	Y233Y (C699T)	-/-	C
CBS	313	-/-	G
CBS	N212N	-/-	C
COMT	H62H	+/+	T
COMT	V158M	+/+	A
COMT	L136L	-/-	C
MAO A	R297R	+/+	T
MTHFR	A222V (C677T)	+/-	HETERO
MTHFR	E429A (A1298C)	+/-	HETERO
MTR	A919G (A2756G)	-/-	A
MTRR	H595Y	-/-	C
MTRR	S175L	+/-	HETERO
MTRR	K350A	-/-	A
MTRR	R415T	-/-	C
MTRR	S257T	-/-	T
MTRR	A919G (A66G)	+/-	HETERO
NOS	D298E	+/-	HETERO
SUOX	S370S	+/+	C
VDR	BsmTaq	+/+	G
VDR	Fok	-/-	C
VDR	Taq	+/+	T

COMT ++
Taq ++

A360A ++
C677T +-
A1298C +-
MTRR +-

ACAT +-
AHCY +-
+-
+-
+-

MTHFR +-
MTRR +-

* No database reference standard available

Genetic Profiling Systems LLC

Client #:

ID #:

Page 1 of 2

(SHMT)

Gene Name	Variation	Result	Call
ACAT1-02	N/A*	To be determined	HETERO
AHCY-01	N/A*	To be determined	HETERO
AHCY-02	N/A*	To be determined	HETERO
AHCY-19	N/A*	To be determined	HETERO
BHMT-01	N/A*	To be determined	A
BHMT-02	N/A*	To be determined	C
BHMT-04	N/A*	To be determined	A
BHMT-08	N/A*	To be determined	C
COMT-61	P199P	To be determined	G
MTHFR-03	P39P	To be determined	HETERO
MTRR-04	L206L	To be determined	T
MTRR-06	V652V	To be determined	G
MTRR-11	A664A	To be determined	HETERO

MTHFR	E429A (A1298C)	+/-	HETERO