Schizophrenia and single-carbon metabolism

Björn Regland *

Institute of Clinical Neuroscience, Göteborg University, Sweden

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Abstract

Schizophrenic patients generally appear to have a disturbed single-carbon metabolism. Methionine and homocysteine are intermediary metabolites in this metabolic system. In a case-control study of the cerebrospinal fluid, a majority of the patients had elevated methionine and a smaller subgroup had elevated homocysteine. Elevated homocysteine is often explained by folate dependency due to mutations in the gene for methylenetetrahydrofolate reductase (MTHFR). A most encouraging feature of single-carbon metabolism is its potential modification by natural means, such as B-vitamins and antioxidants. The findings point to a new area of schizophrenia research: the role of nutrients and antioxidants for rational prevention and treatment.

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1. Introduction

Fifty years ago, a ‘transmethylation’ hypothesis on schizophrenia was proposed, based on the idea of excessive and misdirected transmethylation resulting in the production of psychotoxic methylated metabolites (Osmond et al., 1952). The hypothesis was later modified to rather suggest an insufficient transmethylation process in the patients and was referred to as the ‘one-carbon cycle’ hypothesis (Smythies, 1966). In an attempt to test the original transmethylation hypothesis, a large number of studies were performed in the 1960s and early 1970s to evaluate the effect of methionine in chronic schizophrenia. The administration of methionine yielded varying results, but led to acute psychotic reactions in some 40% of patients. According to Antun et al. (1971), chronic schizophrenics fall into two clear-cut populations: methionine reactors and non-reactors. This intriguing result has unfortunately not (yet) been explained. Schizophrenics evidently differ greatly from healthy in whom methionine, even at 10-g doses, has no behavioural effects (Baldessarini et al., 1979).

Our research interest in single-carbon metabolism emanates from the 1980s. Before 1992, we focused on patients with neurodegenerative dementia disorders (Regland, 1991). However, an alert observation by a psychiatrist (Britt V. Johansson) widened our interest to include schizophrenia and psychotic disorders and appears to have created a new global wave of interest for the ‘one-carbon cycle’ hypothesis.

This article is a review based on our own contributions, in order to describe how the ‘one-carbon cycle’ concept has evolved in the last decade. Two illustrative non-published case reports (Sections 5.2 and 6) are included as they further describe some diagnostic and therapeutic implications.

2. Elevated homocysteine and transient response to cobalamin—a startling observation in a single patient

In 1992, a psychiatrist (Britt V. Johansson) at Uddevalla hospital, Sweden, was seeing a young female patient who had been apparently healthy until the age of 20 and had no family history of psychiatric disorders (Regland et al., 1994).
At this time, she had difficulties in pursuing her University studies and failed her examinations. She had difficulty concentrating, was very tired and often suffered from somatic complaints. She heard voices and had a feeling of being watched. She was treated with neuroleptics with good and almost immediate effect. Later, she had difficulties complying with treatment and became worse and broke all contacts with the psychiatric unit. The next year, her auditory hallucinosis returned, and she displayed paranoid ideas and aggressive outbursts and always carried a knife in her handbag “to defend herself.” At the age of 25, she was admitted to a psychiatric unit against her will and was again treated with neuroleptics. She was treated with haloperidol depot injections every 3 weeks. However, at this time, the antipsychotic effect was only marginal.

The sustained symptoms of hallucinosis described by the patient included auditory and visual disturbances. She heard voices that continually commented on her actions. Her parents’ faces were changed, her room took on an irregular shape, and her clothes looked too big. She was not considered delirious.

Lab results 1. At the age of 25, blood haemoglobin (148 g/L) and the mean corpuscular volume (98 fl) were normal, as was serum folate (13.7 nmol/L). Serum cobalamin (179 pmol/L) was relatively low, although within the references (>150). Serum homocysteine (30.9 µmol/L) was highly increased (upper reference limit <15) in repeated samples.

Because of the increased homocysteine level, and a relatively low serum cobalamin, vitamin B12 (Betolvex®, cyanocobalamin bound to tanninaluminostearate) treatment was started and the homocysteine level was frequently checked (Fig. 1). One milligram per week was administered intramuscularly. After 4–5 weeks, the patient had obviously improved. She became more alert, concentrated better, and was less tired. The hallucinosis was less disturbing.

However, she disliked the intramuscular injections. After 8 weeks, she insisted on stopping this treatment. Two weeks after the last injection, she had deteriorated to the level at which she was before the initiation of cobalamin treatment. She suffered from fatigue and headache, and the grossly disturbing type of hallucinosis was there again. She refused another intensive cobalamin treatment, but accepted 1 mL intramuscularly every 3 months.

Six months later she was still in bad shape, with tiredness and very disturbing hallucinosis. Now she accepted to receive cobalamin injections of 1 mL per week for another 8 weeks. After 2 weeks, there was improvement which remained until the end of the treatment period (Fig. 1).

Three weeks after the last injection, she worsened again and treatment was restarted for yet another period. Within 2 weeks, she again felt better. At that time, however, she exhibited extra-pyramidal side effects and the haloperidol injections were discontinued. From then on, the effect of cobalamin was less evident; in spite of continuous weekly treatment, she actually deteriorated severely. Admission to the hospital was planned in order to recommence neuroleptic treatment. While waiting for this, she received three injections of 1 mL cobalamin in 1 week. There was again dramatic improvement which still remained after 2 months of frequent cobalamin injections, and further treatment with neuroleptics was judged unnecessary.

Lab results 2. A skin biopsy was taken to assess various enzyme activities in the cultured skin fibroblasts. The activities of methylmalonyl-CoA-mutase and methionine synthase were normal. The activity of methylenetetrahydrofolate reductase (MTHFR) was 2.9 nmol/mg protein/h. (The

![Fig. 1. Homocysteine levels from September 1992 to November 1993 in a patient with schizophrenia. Bold lines of the curve indicate the transient increases in homocysteine at times of intensified cobalamin treatment which also concurred with the periods of clinical improvement.](image-url)
mean activity was 6.1 in 15 controls and 3.1 in two controls
with heterozygous MTHFR deficiency).

A few years later, her blood was assessed for mutations in
MTHFR, and she was found to be homozygous for the
normal genetic variant (677C).

In the following years, she refused any further injective
therapy but was supplemented with oral cyanocobalamin
and folic acid. Folic acid did not obviously improve her
response. The concentrations in serum were supra-physio-
logical for both vitamins and would normally be followed by
a decrease of homocysteine to a level less than 10 \( \mu \text{mol/L} \). However, her homocysteine level remained steady around
15 \( \mu \text{mol/L} \), and further supplementation with pyridoxine
(vitamin B6) did not change this. Thus, neither her hyper-
homocysteinaemia nor her mental symptomatology was
completely resolved by oral vitamin supplementation.

3. Elevated homocysteine is a common feature

This case report prompted us to investigate more patients
(Regland et al., 1995). We measured serum homocysteine
levels in 20 consecutive and free-living patients with
schizophrenic syndromes. Sixteen had schizophrenia, three
a schizophreniform disorder and one a schizoaffective
disorder. The patients were compared with 20 mentally
healthy controls who were medical students or belonged to
the hospital staff. The controls were matched for age and
gender and had a mean age of 32 ± 9 years.

The control group had very homogenous homocysteine
levels (mean 11.2 ± 2.1 \( \mu \text{mol/L} \)), with the exception of one
obvious outlier (27.3 \( \mu \text{mol/L} \) who was later explained by
an undiagnosed pernicious anaemia. Based on this control
group, the upper limit of a 95% confidence interval (i.e.,
mean ± 2 S.D.) would be 15.4 \( \mu \text{mol/L} \). Nearly half (9) of the
patients had a homocysteine level above this value!

Five of these nine hyperhomocysteinaemic patients were
women. Because 5 of these patients were on no medication
at all, and 3 of the other 4 had been on neuroleptics for 1–3
months only, the increased homocysteine levels appeared
not to be attributable to psycho-pharmacological medica-
tion. The patients’ diet was not recorded in this study.

4. MTHFR mutation often explains elevated
homocysteine

By 1996, advances in molecular genetics made poly-
morphism analysis relatively easy. The human gene for
MTHFR had been localized to chromosome 1p36.3, and a
677C→T mutation had been identified that results in a
thermolabile variant of MTHFR (Frosst et al., 1995). In its
homozygous form, it reduces the overall enzyme activity (in
vitro) to less than 30% of normal. We therefore investigated
whether this polymorphism was a common cause of
elevated homocysteine in patients with a schizophrenia-like
psychotic disorder (Regland et al., 1997a).

After informed consent, we screened for the MTHFR
genotype (at site 677) in 11 consecutive psychiatric patients
fulfilling two criteria: (1) psychotic disorder of a schizo-
phrenia-like type and (2) increased homocysteine serum
level.

Seven were homozygous and one was heterozygous for
the 677C→T mutation and the remaining three were
normal, i.e., they were homozygous for the most efficient
variant 677C. In the patients who were homozygous for the
677C→T mutation, the homocysteine concentrations did
not respond to vitamin B12 alone but were significantly
lowered (<10) by appropriate supplementation with folic
acid.

Although based on a relatively small number of
observations, it appears likely that elevated homocysteine
in schizophrenia-like patients is often explained by folate
dependency because of homozygosity for the 677C→T
mutation.

5. Homocysteine and methionine in the cerebrospinal
fluid

5.1. In a contrast group (patients with fibromyalgia)

In the mid-1990s, we were intrigued by the chance of
investigating homocysteine metabolism in patients with
fibromyalgia (chronic fatigue and widespread muscle
pain)—a treatment trial for such patients was projected at
our institute (Andersson et al., 1998). The patients were
cronically ill and also had a history rich in infections. The
cerebrospinal fluid (CSF) was investigated in 11 female
patients and compared with 18 healthy female controls of
similar age (Regland et al., 1997b).

The patients’ CSF–homocysteine levels varied between
0.31 and 1.33 \( \mu \text{mol/L} \) (0.61±0.28 \( \mu \text{mol/L} \) (Fig. 2). The
difference between patients and controls (0.19±0.04 \( \mu \text{mol}/
L \) was significant. Concentrations of CSF–methionine and
CSF–cystathionine, respectively, were found to be similar
in patient and control groups.

An important clinical feature of fibromyalgia is fatigu-
ability. This was evaluated with a rating scale including
seven steps. Within the patient group, a positive and
significant correlation was found between CSF–homocys-
teine levels and fatiguability (\( r=0.63; n=11 \)).

5.2. In a psychotic patient (case report)

A 23-year-old self-employed man was mentally healthy
when he sustained a knee injury during a sporting activity
and underwent an operation for several hours, receiving
nitrous oxide for 2 h as part of the anaesthesia setup. He
used to be described as an extrovert and cheerful boy. After
the operation, his mother found him depressed and
Next summer, he fractured his femur in a motorcycle accident. Within 10 days, he underwent two operations. During the first he received nitrous oxide for 20 min and during the second for 3 h. After the operation, he woke up and expressed a feeling of having been “cheated.” He was silent, appeared suspicious and did not chat with those who visited him at the hospital. According to his sister, he cried a lot after these operations. Over the following years, he developed paranoid feelings and harmful ideas towards the responsible surgeon. When he is not forced to use neuroleptics, he would not accept treatment and relapses into paranoid psychosis. During these relapses, he exclaims that the secret service is after him, and he even considers his family members to be KGB agents. At age 30, his mother brought him for further investigations.

**Lab results.** His homocysteine levels in serum (25.6 μmol/L; ref. <15) and CSF (0.72 μmol/L; ref. <0.3) were highly elevated, while the level of methylmalonic acid was normal. CSF-methionine was not analysed.

Unfortunately, he was initially treated only with vitamin B12. A year later, he was found to be homozygous for the 677C→T mutation in MTHFR, indicating a folate dependency. However, because injections with hydroxocobalamin (vitamin B12) had no obvious positive effects, he refused our recommendation to supplement also with folic acid, reflecting his generally suspicious and non-compliant attitude.

In summary, this patient illustrates how one disturbance in homocysteine metabolism (MTHFR mutations) may interact with another (nitrous oxide exposition) and thus trigger neuropsychiatric symptomatology.

Nitrous oxide (N₂O) interacts directly with the transfer of methyl groups because it inactivates cobalamin (vitamin B12) by oxidizing the valency of the cobalt (Co) atom from Co⁺ to Co²⁺ (Banks et al., 1968). The result is inhibition of homocysteine remethylation, which means an even more insufficient transfer of methyl groups in an individual who is homozygous for 677T in MTHFR. The brain is especially vulnerable as it lacks alternative pathways for remethylation (McKeever et al., 1991).

The biochemical effects and the clinical consequences of N₂O exposure have been reviewed repeatedly in anaesthesiological journals (Nunn, 1987; Guttormsen et al., 1994). It seems quite likely that the tolerance of exposure to N₂O during a surgical operation depends upon the patient’s preoperative state (Nunn, 1987).

### 5.3. Case-control study of psychotic patients

A recent paper described methionine and homocysteine levels in the CSF of psychotic patients (Regland et al., 2004). Sixteen women and 20 men (age range 19–54 years) were investigated while hospital in-patients due to acute exacerbations of their psychotic syndromes. They were consecutively included in an on-going study aiming at investigating the CSF in psychotic patients. The diagnoses were validated according to DSM-IV (American Psychiatric Association, 1994). Eighteen patients were diagnosed with schizophrenia (8 paranoid, 7 hebephrenic and 3 with undifferentiated subtypes). Ten patients had a schizoaffective disorder, and 8 patients had a psychotic disorder non ultra descriptum (NUD), i.e., not further described from the psychiatric point of view. The NUD patients had no somatic disorders and no signs of organic brain disorder.
The control group comprised 25 voluntary subjects (age range 18–48 years). They underwent spinal anaesthesia for orthopaedic reasons, which enabled the collection of CSF. The controls were interviewed by a research nurse and found to be healthy from a medical and psychiatric point of view.

**Lab methods.** All patient and control samples were kept in a freezer at −20 °C until analysed 5 years later. The amino acids homocysteine, methionine and cystathionine were determined by gas chromatography mass spectrometry. All samples, from patients and controls, were analyzed simultaneously. Homocysteine concentrations remain stable for up to 10 years in stored plasma kept at −20 °C (Israelsson et al., 1993). We believe that this statement is also valid for CSF. Moreover, there was no correlation between CSF–methionine and storage time. Thus, we have no reason to believe that the outcome of this study was severely biased by the storage time of the samples.

CSF–methionine was significantly higher in patients than controls (Fig. 2). Ten patients had CSF–methionine levels greater than any of the controls (>5 µmol/L). Most had an age of onset around 20 years of age, but one woman developed paranoid schizophrenia starting at age 34. According to the diagnostic criteria of DSM-IV, elevation of CSF–methionine did not distinguish a clinical subgroup of patients. Furthermore, there was no significant difference in CSF–methionine between drug-naive (4.3 ± 1.3 µmol/L; n = 14) and other patients (4.5 ± 1.4 µmol/L; n = 22). All patients, including the drug-naive patients, had significantly higher CSF–methionine than the controls (2.8 ± 1.0 µmol/L). Among controls, there was no difference in CSF–methionine between men and women. Among patients, drug-naive male patients (4.7 ± 1.1 µmol/L; n = 7) had higher CSF–methionine levels than drug-naive female patients (4.0 ± 1.4 µmol/L; n = 7), but not significantly so (p = 0.32). In summary, neither gender nor neuroleptic treatment nor ageing offered an explanation for the increase of CSF–methionine.

The three patients with extremely elevated CSF–homocysteine (Fig. 2) were all young men; a 23-year-old man with onset of hebephrenia at age 16, a 23-year-old man with onset of hebephrenia at age 17 and a 23-year-old man with recent onset of psychosis NUD. CSF–cystathionine was similar in patients and controls. The level was slightly higher in the three patients with elevated homocysteine, but not significantly.

### 6. A case report indicating an additional role for antioxidants?

A 31-year-old woman had been in regular contact with psychiatric medical services since aged 20. She was inclined to severe self-destructive behaviour, including attempted suicide and the mutilation of several fingers. At times of extreme mental strain, she even displayed psychotic symptoms and for a long period was diagnosed as ‘schizophrenic’.

At the age of 25, a GP had found “a low B12 level” and treated her with vitamin B12 injections. She experienced slight but transient improvement. However, her cognitive functions appeared to deteriorate (fatigue, concentration difficulties and memory complaints), and she was later referred to a Memory clinic where folic acid supplementation was added to the treatment. The positive effect was evident, and her well-being improved greatly. As she improved, her diagnosis was questioned and she was considered to have a ‘personality disorder of a border-line type’. At the age of 28 she began to study at the university, and, 3 years later, she is about to complete an advanced education.

**Lab result.** MTHFR genotyping revealed that she has a ‘compound heterozygosity,’ which means that she inherited one allele with the mutation 677C→T and one allele with the mutation 1298A→C, which explains her folate dependency (Chango et al., 2000).

In order to experience full effect of the treatment, for 2 years she was commenced on 30 mg oral folic acid daily in combination with injections of hydroxocobalamin (1 mg subcutaneously) three times a week. However, after adding N-acetylcysteine (NAC) (200 mg ×2) 2 years ago, she has been able to lower the dosage of hydroxocobalamin to one injection every 10th day, and oral folic acid to 10–15 mg daily.

In summary, after treatment with the combination of hydroxocobalamin, folic acid and NAC, her mental health has been remarkably improved and stabilized (for discussion, see Section 7.5).

### 7. General discussion

Disturbances in single-carbon metabolism appear to be related to a variety of neuropsychiatric disorders, covering a broad spectrum from chronic fatigue to depression to psychosis and dementia. This probably reflects the central importance of single-carbon units in brain cellular metabolism.

However, we do not know yet whether an observed disturbance is a primary event that is fundamentally related to the pathogenesis or a secondary phenomenon reflecting a non-pathogenic mechanism. Moreover, there is a third possibility; in addition to a pathogenic mechanism, the observed disturbance might be related to a cofactor that renders a person vulnerable, and, in combination with the fundamental disease-specific factor, triggers the disease or precipitates its course.

Today, very little is known about the fundamental pathogenesis of schizophrenic disorders. We have known for some time that imbalances in the dopamine system (‘the
dopamine theory’) might contribute, but we still do not know whether this is a primary or a secondary phenomenon. Dopaminergic imbalances may be secondary to disturbances in the single-carbon metabolism, and vice versa.

Single-carbon metabolism has an immensely complex influence on biochemical and cellular machinery, including DNA synthesis, gene regulation, membrane fluidity, synaptic function and neurotransmitter synthesis. Imbalances in single-carbon metabolism therefore initiate complex cascades with unforeseeable consequences. Within such complexity, we have identified several disturbances which we have tried to interpret constructively with the hope that we may find a remedy for one of the most devastating human diseases.

7.1. Efficient treatment would be the ultimate 'proof of concept’

Godfrey et al. (1990) showed that methylfolate supplementation significantly improved clinical and social recovery among both depressed and schizophrenic patients in a double-blind, placebo-controlled trial. This promising observation supports a role for insufficient single-carbon metabolism in patients with these disorders.

A positive effect of treatment is usually the most convincing evidence for a ‘proof of concept’, and we were certainly aroused by the fact that our patient (see Section 2) not only displayed a raised level of homocysteine, and a reduced activity of MTHFR, but also responded favourably to cobalamin treatment (Regland et al., 1994). As the increased homocysteine level was reproducible before treatment, the subsequent reduction was apparently a significant effect of cobalamin treatment. However, this clinical effect diminished with time, and the metabolic abnormality was thus not wholly cobalamin dependent. Moreover, there was an apparent discrepancy between homocysteine levels and the alleviation of symptoms in our patient. The homocysteine level normalized during a long period of infrequent injective therapy when there was no alleviation of psychiatric symptoms. Furthermore, the homocysteine level rose transiently when the patient improved psychiatrically during the series of frequent injections (Fig. 1). In conclusion, the patient displayed an insufficient methylation capacity, but the treatment we had chosen was not optimal for this individual. Thus, some other mechanism(s) must also be implicated.

7.2. Homocysteine and MTHFR mutations

Elevated homocysteine in serum is a non-specific risk factor for a variety of disorders, including dementia (Seshadri et al., 2002), vascular disorders and neural tube defects.

CSF-homocysteine concentrations were elevated in all the investigated patients with fibromyalgia, who were chronically fatigued but otherwise mentally healthy, although these results await confirmation. However, it is likely that elevated homocysteine is therefore not specific for schizophrenic patients, not even in the CSF. Instead, the existence of elevated homocysteine in different disorders may reflect different mechanisms and consequences, but elevation of homocysteine can still be a valuable laboratory marker for a subgroup of schizophrenics.

Mutations in the gene for MTHFR may render an individual increasingly dependent on folate and more prone to raised levels of homocysteine. In schizophrenia, our initial finding of a relation to the 677C→T mutation (Regland et al., 1997(a)) has been supported by some studies (Arinami et al., 1997; Joobert et al., 2001; Deng et al., 2002; Sazci et al., 2003) but not all (Kunugi et al., 1998; Virgos et al., 1999). This perhaps reflects the considerable clinical heterogeneity of the schizophrenic population.

Schizophrenic patients with elevated homocysteine appear to consist predominantly of young men (Levine et al., 2002; Applebaum et al., 2004), which is in accordance with our own findings (Regland et al., 2004). In our CSF study, the relative number of patients with elevated homocysteine levels was much lower than was found in our previous study on serum levels. This difference in frequency may depend on chance or on selection criteria for the studies.

7.3. Methionine

The most striking finding of the CSF study is that psychotic patients had elevated methionine, with similar results in all the traditionally diagnosed subtypes. In that study, and after evaluating the possible influence of gender, age, neuroleptic treatment and laboratory methods, we were not aware of any factor that might have confounded the results.

There is no simple and apparent explanation as to why psychotic patients would have elevated CSF-methionine. Excess methionine in brain can theoretically arise for a number of reasons, and might be state dependent, a matter of trait (gene related), or both. We did not check the dietary habits of the patients or the controls. However, increased dietary intake and excessive protein catabolism appear to be less likely explanations. Instead, we consider that increased blood–brain barrier uptake and/or inhibition of methionine adenosyltransferase (MAT), or its cofactors, to be more likely possibilities.

7.4. Blood–brain barrier

The brain is dependent on the local synthesis of methionine as well as the uptake of methionine from blood (Pardridge and Oldendorf, 1977). Interestingly, brain uptake of methionine is high in childhood and then followed by a striking age-dependent decline in maturing humans, which parallel findings in animals (O’Tuama et al., 1991). Age-dependent changes in folate metabolism have been sug-
gested to serve as a triggering event for the onset of schizophrenia (Sharma et al., 1999). It is possible that prospective psychotic individuals fail to adopt the normal decline of brain methionine uptake, when the brain is maturing around the age of 20, and that this results in a state of longstanding methionine brain overload. This may also explain why a substantial number of schizophrenic patients appear to be abnormally sensitive to further methionine loading (Cohen et al., 1974).

7.5. Relation to oxidative stress

Experimental methionine loading brings about various effects on the single-carbon cycle as it lowers serum folate concentration (Connor et al., 1978), induces oxidative stress (Ventura et al., 2000), and lowers the amino acid cysteine (Raijmakers et al., 2003). Cysteine is the rate-limiting precursor in the synthesis of glutathione (GSH), which is the substrate for important antioxidant reactions. Oxidative stress and concomitant impaired antioxidant defence has been shown in drug-naive patients at the onset of non-affective psychosis (Mukerjee et al., 1996; Mahadik et al., 1998). GSH is deficient in red blood cells (Altuntas et al., 2000) and in CSF and prefrontal cortex in the brains of schizophrenic patients (Do et al., 2000). Moreover, GSH is a cofactor for the function of MAT, which is a sensitive target for oxidation, and MAT activity is therefore strongly dependent on cellular GSH levels (Avila et al., 1998).

Although speculative, it is possible that high CSF–methionine in our patients may represent a state of methionine brain overload bringing about depletion of the cofactor GSH and reduction of the MAT activity. MAT has been reported to be significantly underactive in red blood cells (Kelsoe et al., 1982; Smythies et al., 1986; Gomes-Trolin et al., 1998) and in brains (Gomes-Trolin et al., 1998) of schizophrenic patients.

Homocysteine also takes part in redox reactions. The ability of the cobalamin-dependent enzyme methionine synthase to convert homocysteine to methionine is impaired by oxidative stress (McCaddon et al., 2002), and folate can also undergo irreversible oxidation (Fuchs et al., 2001).

The case report in Section 6 may be a good example of how antioxidant therapy can be clinically important when a patient needs increased B-vitamin supplementation. This particular patient was supplemented with NAC, a biologically available form of cysteine and precursor of GSH. As a result of NAC supplementation, the patient was able to reduce the dosages of hydroxocobalamin and folic acid substantially, and yet keep a similar or even improved effect of treatment.

8. Conclusions and future directions

Patients with schizophrenia-like disorders frequently display disturbances in the single-carbon metabolism. Homocysteine itself may exert psychotoxic effects, but should primarily be seen as a useful, though non-specific, laboratory marker of dysfunctional single-carbon metabolism. Elevated methionine may be a similar pathological marker.

It is very unlikely that we will find one single distinct cause for all the disorders in the psychotic spectrum, or even for those within the spectrum of schizophrenia. The obvious clinical heterogeneity probably reflects a variety of mechanisms.

MTHFR is a minute component in the complex system of single-carbon metabolism, and this may explain why the significance of MTHFR is weak, or even absent, in some studies. However, if MTHFR mutations are significantly overrepresented in the family of schizophrenic disorders, this strongly supports the mutation as a primary contributing factor, either because it makes the person vulnerable for developing the disease under certain circumstances, or that it modifies a disease which would have evolved anyway. If this is true for MTHFR, we have every reason to believe that this also holds true for many other possible components in single-carbon metabolism. In this regard, MTHFR mutations merely represent ‘the tip of the iceberg’.

In summary, our present knowledge is as follows: single-carbon metabolism is important for brain function and may dysfunction in a variety of ways, eventually resulting in neuropsychiatric disease of various typologies, which themselves are dependent on genetics, toxicology (for example, nitrous oxide) and age.

An individual’s age may be a risk because of specific age-related mechanisms. Schizophrenia is related to age as it is most often characterized by an onset in the (fragile) end of the teenage period, when the brain is reaching its final maturation. This fact may in itself be an important clue to a better understanding of why and how this particular disease evolves. From this perspective, and according to the findings by O’Tuama et al. (1991), the role of the blood–brain barrier must be better understood. On the whole, we also need better tools for direct studies of single-carbon metabolism inside the brain. For the time being, PET-scan might be the most advanced tool for such investigations (and is not yet exploited for this purpose).

A most encouraging feature of single-carbon metabolism is its potential modification by natural means, such as B-vitamins and antioxidants. Our findings in this field point to a new area of schizophrenia research: the role of nutrients and antioxidants for rational prevention and treatment. In order to achieve ‘proof of concept,’ we need well-performed clinical trials.

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