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REVIEWS: CURRENT TOPICS

Folate and long-chain polyunsaturated fatty acids in psychiatric disease

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Abstract

Schizophrenia, autism and depression do not inherit by Mendel's law, and the search for a genetic basis seems unsuccessful. Schizophrenia and autism relate to low birth weight and pregnancy complications, which are associated with developmental adaptations by "programming". Epigenetics might constitute the basis of programming and depend on folate status and one-carbon metabolism in general. Early folate status of patients with schizophrenia might be compromised as suggested by (i) coinciding incidences of schizophrenia and neural tube defects (NTDs) in the Dutch hunger winter, (ii) coinciding seasonal fluctuations in birth of patients with schizophrenia and NTDs, (iii) higher schizophrenia incidence in immigrants and (iv) higher incidence in methylene tetrahydrofolate reductase 677C→T homozygotes. Recent studies in schizophrenia and autism point at epigenetic silencing of critical genes or chromosomal loci. The long-chain polyunsaturated fatty acids (LCPUFA), arachidonic acid (AA, from meat) and docosahexaenoic acid (fish) are components of brain phospholipids and modulators of signal transduction and gene expression. Patients with schizophrenia and, possibly, autism exhibit abnormal phospholipid metabolism that might cause local AA depletion and impaired eicosanoid-mediated signal transduction. National fish intakes relate inversely with major and postpartum depressions. Five out of six randomized controlled trials with eicosapentaenoic acid (fish) have shown positive effects in schizophrenia, and 4 of 6 were favorable in depression and bipolar disorders. We conclude that folate and LCPUFA might be important in both the etiology and severity of at least some psychiatric diseases.

Keywords: Schizophrenia; Autism; Depression; Folate; One-carbon metabolism; Long chain polyunsaturated fatty acids; Epigenetics

1. Introduction

The stable cross-cultural and cross-racial incidence of schizophrenia, initially noticed by the World Health Organization (WHO) in 1970, suggests that schizophrenia susceptibility genes have been with us since the origin of *Homo sapiens* some 160 000 years ago. This, together with the lower fecundity of, notably male, schizophrenics raises the question why the disease has survived natural selection [1,2]. Family studies of schizophrenics indicate that schizophrenia is rarely the only psychiatric illness, but that there is a continuum of disorders that is likely to derive from the combination of a small number of susceptibility genes, with intermediate outcomes such as "schizotypy," depression, bipolar disorders, sociopathy and learning disabilities (including dyslexia). These genes might have been conserved during evolution because they actually code for exceptional creativity and intelligence. There is a long list of famous musicians, writers, philosophers, scientists and inventors with schizophrenic or schizotypal characteristics [2]. Our rapidly changing lifestyle, beginning with the agricultural revolution (commencing some 10 000 years ago), and its acceleration since the industrial revolution (beginning some 200 years ago) might have turned this "advantageous genotype" into a disadvantage. The WHO predicts psychiatric disease, notably depression, to be ranking in the top of chronic diseases in Western countries in the near future. The present consensus is that the prevalence of autism exhibits an increase that is unlikely to be explained by changes in diagnostic criteria or improvements in case ascertainment. It is, e.g., estimated that the prevalence in the United States has shown a >10-fold increase in the past decades, with <3 cases per 10 000 children in the 1970s to >30 per 10 000 in the 1990s [3].

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The rapidly increasing incidence, and perhaps severity, of some psychiatric diseases suggests that, analogous to other typically Western diseases such as coronary artery disease, diabetes mellitus type 2 and some cancers (e.g., prostate, breast, colon, or lung), we are dealing with a conflict between our contemporary lifestyle and our slowly adapting genome. We review the currently available data in support of the hypothesis that (early) environmental factors, notably those of nutritional nature, play an important role in the etiology and severity of at least some psychiatric diseases. Emphasis is laid on the role of folate and long-chain polyunsaturated fatty acids (LCPUFA) in the etiologies of schizophrenia and autism and the role of dietary folate and LCPUFA in the severity of schizophrenia and depression.

2. Influence of genetics, birth weight and pregnancy complications

Psychiatric diseases, such as schizophrenia (1% of population) and autism (0.1% of children), are among the "complex" diseases that, by definition, do not inherit by Mendel's law. They are generally considered to derive from a combination of heritable and environmental factors. Currently, autism holds a respectable list of over 89 candidate genes, provoking the comment that "as of this date, no gene has been proven to *not* be an autism disease gene" [4]. Also, the list of schizophrenia candidate genes is on steady growth, while genes alone cannot explain the 2.7 times higher schizophrenia relative risk of first generation migrants and the 4.5 times higher relative risk of second generation migrants, which notably affect subjects migrating from the developing to developed countries [5].

The higher concordance of monozygotic twins for schizophrenia (about 50%; [6]) and, notably, autism (60–90%; [7]), as compared with dizygotic twins (schizophrenia: 17%; autism: 0–10%), seems to argue in favor of the importance of genetic factors. Twin studies in support of a genetic background have, however, been seriously criticized because of methodological problems and questionable assumptions [8]. Taking chorionicity into account, it was found that simple monozygotic concordance rates may overestimate schizophrenia heritability, with low birth weight and notably "programming" probably being of more importance [9,10].

Birth weight has only a small genetic component and reflects mainly the quality of the intrauterine environment [11]. Small and disproportionate babies derive from a dysbalance between fetal nutrient demand and maternoplacental nutrient supply in early and late gestation, respectively, causing what is named the "thrifty phenotype" [12]. The underlying process of programming stems from a stimulus or an insult at a sensitive or critical period of development with long-term consequences. Programming is a well-known phenomenon in biology. The underlying mechanism contributes to "developmental plasticity" [13]. Its occurrence is not limited to an adverse environment in intrauterine life that stems from under or malnutrition, but it may also be triggered by infection, season of birth and smoking, or adverse environmental conditions in early infancy. By down-regulation of growth and the induction of other developmental adaptations, it is now presumed to affect many tissues, organs and systems, including the central nervous system. Such adaptations may be beneficial for short-term survival but are, in the long-term, notably when stimulated by unfavorable postnatal lifestyle, implicated in a number of chronic noncommunicable diseases at adult age, including schizophrenia [12,14]. A recent study showed that at adolescent age, very-low-birth-weight babies are at risk for developing psychiatric symptoms and reduced social and academic skills, while term small-for-gestational-age babies have higher risk of emotional, behavioral and attention deficit symptoms [15]. A study of perinatal risk factors for autism among cases, unaffected siblings and controls in W-Australia concluded that we might be dealing with genetic factors that predispose to obstetric complications and that these factors may precipitate to autism by exposure to certain environmental stimuli [16]. Similar perinatal risk factors, including low birth weight, but also parental psychiatric history, were reported in another recent autism case-control study [17]. A meta-analysis of prospective population-based studies revealed that schizophrenia is associated with complications of pregnancy as well [18].

Taken together, the available data suggest that birth weight, pregnancy complications and parental psychiatric history might be important to the development of at least some psychiatric diseases. The plausibility of causality would, however, benefit greatly from the identification of the offending environmental factors and the elucidation of the underlying pathophysiological mechanism(s). Recent developments have shed more light into these issues.

3. Nutritional factors in the etiology and severity of psychiatric disease

Indications in favor of nutritional factors in prenatal life as causative factors in psychiatric disease derive from the two times higher incidence of schizophrenia in the Dutch offspring cohort that was conceived in the last month of the 1944–1945 Dutch hunger winter [19]. The schizophrenia incidence in this cohort coincided with a 2.5 times higher incidence of neural tube defects (NTDs), which suggests involvement of low folate status. The approximately two times higher schizophrenia relative risk associated with maternal undernutrition was recently confirmed in a study of the massive 1959–1961 famine in China [20]. Folate involvement is further strengthened by the demonstration of coinciding seasonal fluctuations in birth incidence of patients with NTDs and schizophrenia, with both disorders exhibiting highest conception rates in May–June [21]. A third indication of folate involvement may come from the study of immigrant populations. Immigrants are less likely to use folic acid supplements preconceptionally and in the

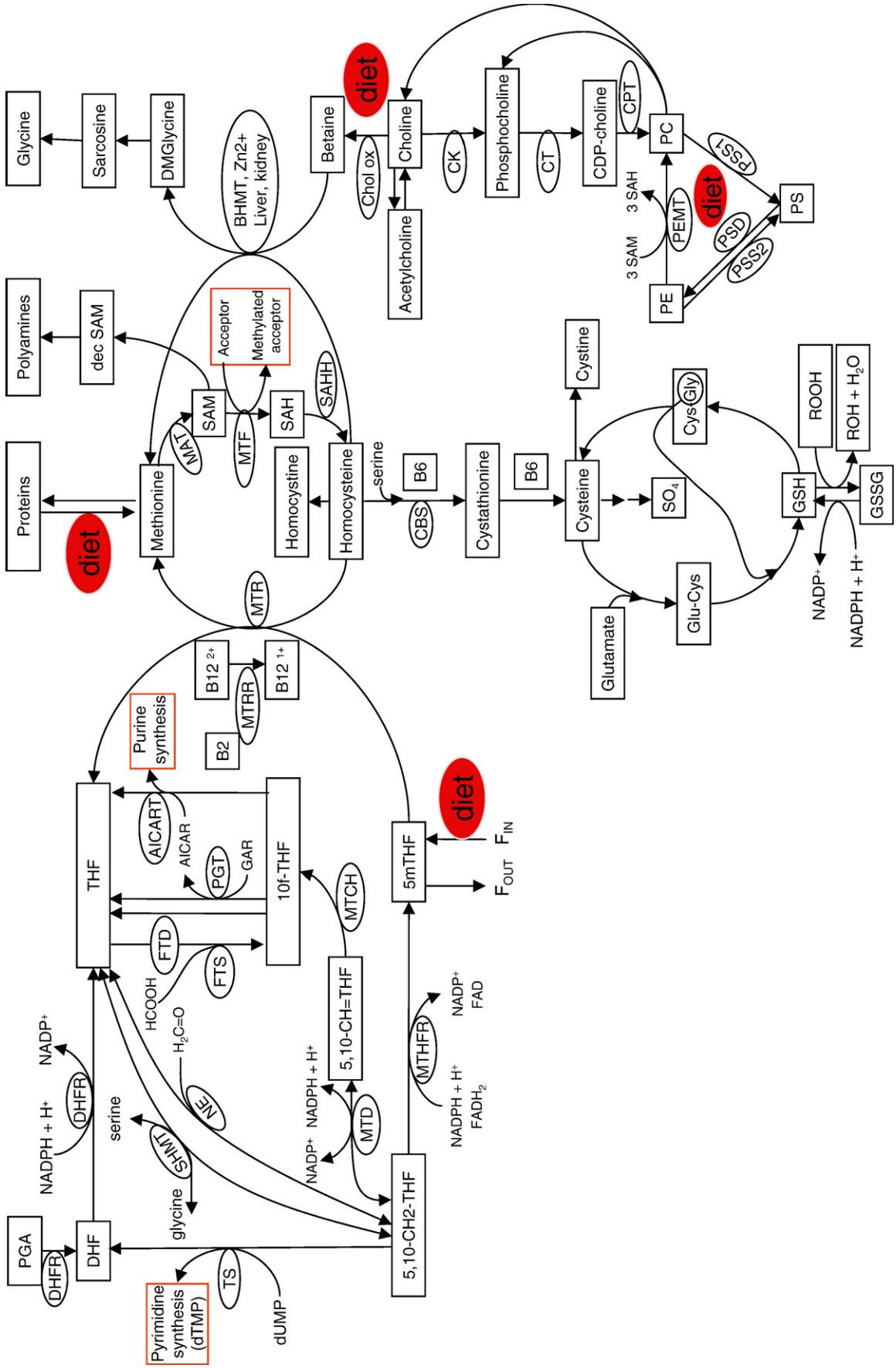
first trimester [22–25], and they also have higher NTD rates [23]. Both of these seem to relate to the alarmingly higher incidence of schizophrenia in the second-generation offspring [5]. A recent metastudy of 2265 schizophrenia cases and 2721 controls revealed that the homozygous methylene tetrahydrofolate reductase (MTHFR) 677C→T variant is characterized by a 1.36 (1.07–1.72) higher odds ratio for schizophrenia, as compared with the wild-type CC [26]. MTHFR TT homozygotes are in need of higher folate status for similar MTHFR functioning, compared with CT and CC counterparts, because of the thermolability and reduced activity of the MTHFR 677C→T enzyme [27]. Finally, Moretti et al. [28] reported on a 6-year-old girl with cerebral folate deficiency, developmental delay, psychomotor regression, seizures, mental retardation and autistic features, who, after one year of folinic acid supplementation, responded favorably with regard to neurological development to exhibit "classic" autistic features. Other indications in favor of nutritional imperfections in pregnancy and early postnatal nutritional status derive from the association between short birth intervals and schizophrenia in the offspring [29] and the association of schizophrenia with the total number of siblings per household during childhood [30].

Patients with schizophrenia living in "developing countries" have consistently been found to have a differential advantage in course and outcome of the disease, which is probably on account of environmental factors and, notably, diet [31]. Schizophrenia runs a more severe course in countries with a relatively high saturated fat intake and low unsaturated fat intake [2,32]. Many studies of patients with schizophrenia have shown low circulating folate and mildly increased homocysteine [33–36] and, occasionally strongly, impaired LCPUFA status, including ω3LCPUFA status [37,38]. Serum folate concentrations in patients with schizophrenia correlate inversely with the severity of negative symptoms [34], while a randomized controlled trial with methylfolate in patients with major depression or schizophrenia improved both clinical and social recovery [39]. The picture emerges that low folate status or, possibly, abnormal one-carbon metabolism, in general, and low polyunsaturated fatty acid status might be among the offending factors that are involved in both the etiology and the severity of at least some psychiatric diseases.

4. Folate, one-carbon metabolism and epigenetics

Epigenetics refers to modifications in gene expression that do not entail a change of DNA sequence. The discipline studies heritable, but potentially reversible, changes in gene expression by DNA methylation and alterations of chromatin structure [40–44]. DNA methylation makes use of *S*-adenosylmethionine (SAM) as a substrate. SAM is the methyldonor of over 80 methylation reactions known to date, and many micronutrients, including those in the folate cycle, are indirectly involved in its synthesis from the essential amino acid methionine (Fig. 1). SAM-substrated DNA methylation by DNA methyltransferases is predominantly directed at CpG dinucleotides, in which the cytosine is converted to 5-methylcytosine. These CpGs tend to occur in "islands" that are abundant in promoter regions of genes that are regulated in their expression by methylation. Epigenetic modification of chromatin structure occurs by SAM-substrated methylation of histones and also by their acetylation, phosphorylation and ubiquitylation. Different phenotypic characteristics of somatic cells within a single organism provide a lively example of the biological importance of the resulting "epigenotype" of which much is based on gene-silencing by DNA methylation, or, alternatively, on gene activation through methylation of suppressor genes. Most somatic cells are, in this manner, "locked" into specific patterns of gene expression, which provides the basis of cell differentiation and thereby the typical characteristics of, e.g., a hepatocyte or neuron. Analogous to the memory contained within a liver cell that it is to remain a liver cell even after mitosis, it has been suggested that synaptic input or other environmental stimuli lead to epigenetic changes that are at the basis of synaptic plasticity and, thereby, the formation of long-term memory and adjustment of neural functioning [45].

It has, for long, been believed that epigenetic modifications that are acquired during the life of an animal are erased during gametogenesis (i.e., meiosis) to restore the totipotency of the fertilized egg and that these modifications can therefore not be transmitted to the next generation. This proved, however, incorrect for at least some mammalian alleles (so-called metastable epialleles), and it is now clear that through this mechanism, phenotype can be inherited by events that are mostly considered stochastic in nature. Transgenerational inheritance of the epigenetic state conserved in meiosis is distinct from parental imprinting and from epigenetic maintenance during mitosis. Following erasure of epigenetic marks during meiosis, parental imprinting entails epigenetic silencing of an allele according to the sex of the animal. It causes "parent-of-origin specific effects" that derive from monoallelic expression in somatic cells of the offspring and in which the epigenetically inactivated gene may derive either from the mother or father. Mitotic epigenetic maintenance, on the other hand, refers to the propagation of the epigenetic state during cell division. The fidelity of DNA methylation maintenance in dividing cultured mammalian cells amounts to 97–99.9% per mitosis, whereas the de novo methylation amounts to 3–5% per mitosis [43]. The changes in the epigenome following mitosis, driven by (e.g., hormone-initiated) developmental programs of cell and tissue differentiation, aging, microenvironment but also stochastic events, may induce further variation in the ultimate phenotypic characteristics. It has, e.g., recently been established that with advancing age, monozygous twins may exhibit deviant gene activities that trace down to epigenotypic differences [46]. Phenotypic adjustment by epigenetic modification, together with long-term adjustment of DNA base-sequence by


Glycine
Sarcosine
DMGlycine
BHMT, Zn2+
Liver, kidney
Betaine
diet
Chol ox
Choline
CK
Phosphocholine
CT
CDP-choline
CPT
PC
PSS1
PS
PSD
PSS2
PE
PEMT
3 SAM
3 SAH
Acetylcholine
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Acceptor
Methylated acceptor
Proteins
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Methionine
MAT
SAM
MTF
SAH
SAHH
Homocysteine
serine
Homocystine
B6
CBS
Cystathionine
Cystine
Cysteine
SO4
Cys-Gly
GSH
ROOH
ROH + H2O
GSSG
Glutamate
Glu-Cys
NADP+
NADPH + H+
MTR
B12 2+
B12 1+
MTRR
B2
Purine synthesis
AICART
AICAR
PGT
GAR
THF
10f-THF
FTD
FTS
HCOOH
MTCH
5mTHF
diet
FIN
FOUT
H2C=O
NE
serine
SHMT
glycine
5,10-CH=THF
NADPH + H+
NADP+
MTD
MTHFR
NADP+
FAD
NADPH + H+
FADH2
5,10-CH2-THF
PGA
DHFR
DHF
NADPH + H+
NADP+
DHFR
TS
dUMP
Pyrimidine synthesis (dTMP)

mutation and short-term adjustment by interaction with the environment through transcription factors, is at the center of our ability to adapt to the "conditions of existence" which, on its turn, constitutes the major driving force of evolution. Any change of environment (e.g., current lifestyle) beyond the flexibility of base-sequence, epigenetics or physiological interaction with nuclear transcription factors, puts us at risk of disease development.

Epigenetic deregulated (otherwise perfectly normal) genes, or combinations of these with disease susceptibility genes, are more likely to be at the basis of complex diseases than gene mutations or polymorphisms *per se*. Epigenetic deregulation may notably account for the incomplete penetrance, such as encountered in autism and schizophrenia. Parent of origin-specific gene regulation by imprinting and triggers like gender (i.e. hormones) and endocrine rearrangements during life, may unfavorably affect epigenetic status and thereby explain [40,44] the relation of complex diseases with low birth weight and obstetric complications (autism and schizophrenia), gender inequality (male/female=4 in autism), as well as the late onset, the peak periods of onset during life and the fluctuating course of psychosis in schizophrenia [43]. Parent-of-origin imprinting and hormones are well known factors to affect epigenetic status, but nutrition also proved intimately involved in epigenetic status and its heritability. The latter was elegantly demonstrated by Waterland and Jirtle [47,48] who studied the influence of "methylation diets" on phenotype. They supplemented female mice with extra folic acid, vitamin B_{12}, choline and betaine (see Fig. 1) from 2 weeks prior to conception until weaning to show augmented methylation of a retroviral element within the so-called "agouti-gene", which is a gene that determines the color of their coat. The intervention (partially) silenced the agouti-gene by methylation and thereby caused the coat color of the offspring to shift permanently from yellow into the brownish (pseudo-agouti) phenotype, while there was also evidence of transgenerational transmission. Another study emphasized the importance of homocysteine and *S*-adenosylhomocysteine (SAH). These are products of SAM methylation (Fig. 1) and SAH is a potent inhibitor of methyltransferases. In this study, Friso et al. [49,50] showed that genomic DNA methylation correlates directly with folate status and inversely with levels of plasma homocysteine. The study group was a mixed population of patients with and without coronary artery disease and, consistent with MTHFR activity, the encountered association of global DNA methylation with folate tracked down to lower DNA methylation in MTHFR 677C→T homozygotes with low folate status [49]. Their results suggest that interaction between nutritional status and genetic polymorphism has the potential to modulate gene expression through DNA methylation [49,50]. A study of Ingrosso et al. [51] with hyperhomocysteinemic patients on hemodialysis revealed global and locus-specific DNA hypomethylation, which was probably mediated by the associated increase of the methyltransferase inhibitor SAH. Importantly, subsequent folic acid supplementation augmented both global and locus-specific DNA-methylation, as derived from the switch from abnormal biallelic expression to normal monoallelic expression for a number of genes with known sensitivity to methylation. The study showed that folate status affects the expression of sex-linked and imprinted genes, which are both characterized by the expression of specific alleles, and that these effects are not limited to early life. A recent study of Lillycrop et al. [52] showed that dietary protein restriction of pregnant rats, a well known model that reduces fetal growth, causes lower methylation status and activation of the genes for the glucocorticoid receptor and peroxisome proliferator-activated receptor (PPAR)-alpha in

Fig. 1. One-carbon metabolism and its immediately surrounding metabolic pathways. Indicated are the folate cycle (top left), the methionine–homocysteine cycle (top middle), the transsulphuration pathway and its connection with cystathionine/glutathione synthesis (middle and middle-bottom), the betaine–homocysteine regeneration pathway (top right) and the choline–betaine connection with phospholipid synthesis and phospholipid interconversion (top right and top middle to bottom). One-carbon metabolism might play an important role in epigenetics, which refers to modification of gene expression that do not entail a change of DNA base sequence. Epigenetics studies heritable, but potentially reversible, changes in gene expression by DNA methylation and/or alteration of chromatin structure. DNA methylation occurs by SAM-substrated methylation of cytosine bases in notably CpG sequences and is catalyzed by DNA methyltransferases. Dysbalances in one-carbon metabolism may cause altered states of DNA methylation and, thereby, phenotypic changes that, in early life, are connected with developmental plasticity and that, at later life, are associated with complex diseases, including cardiovascular disease, some cancers and psychiatric disease. 10f-THF, 10-formyltetrahydrofolate; 5,10-CH_THF, 5,10-methenyltetrahydrofolate; 5,10-CH2-THF, 5,10-methylenetetrahydrofolate; 5mTHF, 5-methyltetrahydrofolate; AICAR, aminoamidazolecarboxamide ribotide; AICART, aminoimidazolecarboxamide ribotide transformylase; B2, vitamin B_2 (flavin adenine dinucleotide); B12, vitamin B_{12} (methylcobalamin) ($^{1+}$ and $^{2+}$ refer to oxidation state of cobalt atom); B6, vitamin B_6; BHMT, betaine homocysteine methyltransferase; CBS, cystathionine β-synthase; CDP, cytidine diphosphate; Chol ox, choline oxidase; CK, choline kinase; CPT, CDP-choline, 1,2-diacylglycerol cholinephosphotransferase; CT, CTP-phosphocholine cytidylyltransferase; Cys, cysteine; Cys-Gly, cysteinylglycine; decSAM, decarboxylated *S*-adenosyl methionine; DHF, dihydrofolate; DHFR, dihydrofolate reductase; DMGlycine, dimethylglycine; dTMP, thymidine monophosphate; dUMP, 2'deoxyuridine monophosphate; FAD(H2), oxidized (reduced) flavin adenine dinucleotide (vitamin B_2); *F*in and *F*out, the rates at which 5mTHF enters and leaves the cell, respectively; FTD, 10-formyltetrahydrofolate dehydrogenase; FTS, 10-formyltetrahydrofolate synthase; GAR, glycinamide ribotide; Glu, glutamine; Glu-Cys, glutamylcysteine; Gly, glycine; GSH, reduced glutathione (Glu-Cys-Gly); MAT, methionineadenosyltransferase; MTR, methionine synthase; MTCH, 5,10-methylenetetrahydrofolate cyclohydrolase; MTD, 5,10-methylenetetrahydrofolate dehydrogenase; MTF, methyltransferases (including DNA methyltransferases); MTRR, methionine synthase reductase; NADP(H), oxidized (reduced) nicotinamide adenine dinucleotide phosphate; NE, nonenzymatic interconversion of THF and 5,10-CH2-THF; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PEMT, phosphatidylethanolamine *N*-methyltransferase; PGA, pteroyl-L-glutamic acid (folic acid); PGT, phosphoribosyl glycinamidetransformylase; PS, phosphatidylserine; PSD, phosphatidylserine decarboxylase; PSS1 and 2, phosphatidylserine synthase; ROOH, peroxide; SAHH, SAH hydrolase.

the livers of their offspring. These receptors are important in embryogenesis and in postnatal blood pressure and metabolic control and are among the many candidates to be involved in fetal programming. The observed changes proved persistent up to at least 6 days after weaning and could be prevented by fortification of the protein-restricted diet with folic acid. The study showed that abnormal 'methyl' status of specific genes in specific tissues, as induced by an unbalanced diet, might be at the basis of phenotypic changes in early development [52]. Other causes may be reduced uterine blood flow, maternal postnatal behavior and social interaction [53]. The altered epigenotype might persist throughout the life span, passed on to the next generation, and one-carbon metabolism might be central from a mechanistic perspective.

There is as yet no solid evidence of epigenetic factors in schizophrenia. The disease has, however, been linked to prenatal deficiencies of folate (see above), vitamin B_6 and vitamin B_{12} [29], which are micronutrients that are either directly or indirectly involved in one-carbon metabolism and, thereby, in gene expression and repression through methylation (Fig. 1). Petronis et al. [54] conducted a pilot study on the epigenetic status of the 5′ -regulatory region of the dopamine D2 receptor gene (DRD2). DRD2 has been listed as a candidate gene for schizophrenia susceptibility, and DRD2 antagonism is common to all antipsychotics. They studied two pairs of monozygous twins, one concordant and one discordant for schizophrenia. It appeared that the affected twin from the pair discordant for schizophrenia was epigenetically "closer" to the affected concordant twins than to his unaffected monozygous cotwin, suggesting that schizophrenic patients have similar epigenetic status of DRD2. Schizophrenia symptomatology is already, for some time, known to become exacerbated by high doses of methionine (Fig. 1) [55]. Mice receiving prolonged treatment with methionine exhibit behavior patterns that mimic specific phenotypic aspects of schizophrenia, and this coincides with augmented brain contents of SAM, hypermethylation of the reelin promoter and down-regulated expression of both reelin and glutamic acid decarboxylase (GAD_{67}). Both reelin and GAD_{67} carry CpG islands in their promoter regions, and the degree of reelin methylation in this region correlates inversely with reelin expression [56,57]. The reelin protein is necessary for neuronal migration, axonal branching, synaptogenesis and cell signaling, while GAD_{67} is one of the two isoenzymes that synthesize the neurotransmitter gamma-aminobutyric acid. Several studies have shown reduced reelin mRNA and protein levels in postmortem brains of patients with schizophrenia and also in patients with bipolar disorders [58]. Recent studies of postmortem brains of schizophrenic patients and controls revealed reelin gene promoter hypermethylation and down-regulation of reelin and GAD_{67} expression, suggesting an epigenetic basis for their hypoactivity in schizophrenia [58–60]. Also, postmortem brains of autistic patients contain low levels of the reelin mRNA and protein which, together with some other anomalies, suggest impairment of the reelin signaling pathway in autism as well [61]. Iwamoto et al. [62] reported a tendency towards a highly methylated state of the CpG island of the *SOX-10* gene in the brains of patients with schizophrenia. The *SOX-10* gene codes for an oligodendrocyte-specific transcription factor, and it was found that the percentage methylated allele correlated inversely with relative *SOX-10* expression. Catechol-O-methyltransferase (COMT) is a strong candidate in the etiology of schizophrenia. Methylation of the promoter of soluble COMT in the brain of patients with schizophrenia was ruled out as a common cause, but one patient with extreme negative symptoms showed the unique feature of full methylation of the 23rd cytosine [63]. James et al. [64] reported on 20 children with autism and 33 controls in which they studied the plasma concentrations of several metabolites in the methionine transmethylation and transsulfuration pathways (Fig. 1). In autism, they found higher SAH, adenosine and oxidized glutathione (GSSG) in conjunction with lower methionine, SAM, SAM/SAH ratio, homocysteine, cystathionine, cysteine, total glutathione and total glutathione/GSSG ratio. This profile is consistent with lower methylation capacity (i.e., lower SAM/SAH ratio) and increased oxidative stress (relatively increased GSSG) and proved correctable by supplementation with folinic acid, betaine and methylcobalamin. A recent study by Lamb et al. [65] identified two discrete loci underlying linkage of autism to chromosome 7 with possible parent-of-origin specific effects and a role of (an) imprinted gene(s). The involvement of *epigenetic* rather than *genetic* variation might explain the lack of causative base-sequence variants so far identified in candidate genes in these regions. It may be concluded that the number of studies on the epigenetic basis of psychiatric disease and the number of investigated patients is, as yet, small. Multiple genes might be involved, given the possible heterogeneity of what is presently considered to be single disease entity and given a possible multihit etiology that starts in the maternal uterus or perhaps even prior to conception up to oogenesis in the grandmaternal womb.

5. Long chain polyunsaturated fatty acids and brain development

Low status of LCPUFA ($\geq$20 carbon atoms and $\geq$3 methylene-interrupted *cis* double bonds) may play a role as one of the offending factors in both the etiology of psychiatric disease and its severity. LCPUFA are either of the ω6 or ω3 series. Qualitatively and quantitatively important LCPUFA are arachidonic acid (AA, an ω6LCPUFA notably from meat), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (both ω3LCPUFA from fish) [66,67]. They derive from the parent essential fatty acids (EFA) linoleic and alpha-linolenic acids, and some of the C_{20} members (i.e. AA, EPA and dihomo-gamma-linolenic acid) are precursors to eicosanoids (pros-

taglandins, thromboxanes, and leukotrienes). LCPUFAs are building blocks of membrane phospholipids of all cells, in which they contribute to the physical properties of the membrane and to (synaptic) signal transduction. EFAs make up 20% of brain dry weight, including about 6% for AA and 8% for DHA. DHA and AA are determinants of membrane fluidity, which is important for the efficacy of neurotransmitter-receptor interaction and transporters. AA is of special importance as a second messenger in signal transduction [68]. DHA is the major structural lipid of the retinal photoreceptor outer segment membrane, where its fluidity is essential to accommodate the extremely rapid conformational changes of rhodopsine [68]. Both AA and DHA are important to maintain a healthy endothelium of our cardiovascular system [69,70], of which the brain is obviously dependent for adequate nourishment. LCPUFA synthesis from the parent precursors may be subject to programming that affects the vascular endothelium. A high-saturated-fat diet given to pregnant rats caused reduced AA and DHA and increased linoleic and alpha-linolenic acids in the aorta of their offspring, suggesting poor conversion of precursor EFA to LCPUFA. These abnormalities coincided with vascular dysfunction and persisted to adulthood [71].

LCPUFA are not only important membrane structural elements, but, together with their eicosanoid products, they are also firmly implicated in gene expression. For example, dietary LCPUFA are ligands to PPARs and suppress the expression of sterol regulatory element binding proteins. These are nuclear transcription factors that can be considered as main switches in the coordinated expression and repression of a variety of (key) enzymes in intermediary metabolism, thermoregulation, energy partitioning, growth and differentiation and inflammatory responses [72–75]. "Nutrigenomics" studies in rats revealed that ω3LCPUFA (i.e., notably EPA and DHA) modulate the expression and repression in brain of a sizeable number of genes that are involved in structure, energy metabolism, neurotransmission, signal transduction and regulation [76,77]. Dietary LCPUFA also influence neurotransmitter physiology. Experiments with rats showed that fish oil supplementation influences several neurochemical and behavioral features of monoaminergic function, causing a 40% higher dopamine content in the frontal cortex, a reduction of monoamineoxidase-B activity, greater binding to DRD2 and 25% lower ambulatory activity as compared to controls [78].

LCPUFA-rich fresh- and salt-water shoreline-based diets are likely to have been at the basis of our larger and more sophisticated brains, compared with other primates. A constant dietary LCPUFA supply and notably that of DHA might therefore be important [79–87]. DHA might at least be conditionally essential, since we have limited ability for its synthesis from the parent essential fatty acid alpha-linolenic acid [88–91]. Higher dietary DHA intake may on its turn require higher AA intake to prevent competition between ω3LCPUFA and ω6LCPUFA, while alpha-linolenic acid has an independent role as a precursor to cholesterol synthesis in brain [92]. This lays emphasis on a dietary ω3/ω6 balance [66,67,93,94], a balance that, since the industrial revolution, has increasingly become violated in favor of higher intake of ω6 fatty acids (notably linoleic acid), decreasing intake of ω3 fatty acids and increasing intake of saturated and *trans* fatty acids [94]. Deficiency of ω3 fatty acids in primates is, amongst other conditions, associated with psychiatric pathology [95] and with reduced learning, abnormal electroretinograms and visual impairment in humans [96]. AA and DHA status in preterm babies is related to birth weight, head circumference and length at birth [97–100], and both AA and DHA may be protective against the central nervous, visual and auditory damage that is typical for (very) premature babies [101]. Various studies have shown suboptimal neurodevelopment of both preterm and term babies receiving infant formulas without LCPUFA, although many of these effects might be transient [102–108]. It is clear that LCPUFA have important functions in brain and that notably the low ω3LCPUFA status of the contemporary Western diet might put us at risk of suboptimal brain development and functioning.

6. Schizophrenia-phospholipid hypothesis

There are (anecdotic) reports that (i) feverish illness in schizophrenics ameliorates their psychiatric symptoms, (ii) schizophrenics rarely suffer from rheumatoid arthritis (suggesting a generalized reduced inflammatory response), (iii) schizophrenic patients are less capable of producing the typical (prostaglandin-induced) cutaneous flush that follows nicotinic acid ingestion or topical application and (iv) schizophrenia in developing countries with higher LCPUFA intakes runs a less severe course [2,31,32,109]. Horrobin [2] linked these observations to develop the so-called phospholipid hypothesis that states that schizophrenia is a systemic disease with a central theme of impaired AA release and consequently insufficient production of its eicosanoid metabolites to support adequate signal transduction [110]. In other words, we are possibly dealing with a genetically determined generalized "abnormality" of phospholipid metabolism that might be sensitive to prevention or correction by nutritional factors. These nutritional factors are likely to be LCPUFA, of which the intake has been subject to tremendous decline since the industrial revolution. Lower contemporary intake in Western countries is, e.g., suggested by the relatively high AA and DHA status of Tanzanian women who consume an AA and DHA-rich, fresh water fish-based diet that (in this respect) is likely to be close to our ancient diet [111]. It is possible that the genetic makeup of patients with schizophrenia would, in the past, not have precipitated to disease and that the LCPUFA-rich diet of our ancestors enabled them to take full evolutionary advantage of the associated intelligence and creativity [2].

Consistent with the increased LCPUFA losses postulated by the phospholipid hypothesis, both patients with schizo-

phrenia [32,112] and autism [113] have increased activity of phospholipase A_2, which releases AA from membrane phospholipids (a process vital to brain cell signaling), while their LCPUFA in erythrocytes appear more sensitive to oxidative stress in vitro [113,114]. Brain magnetic resonance spectroscopy studies in schizophrenics showed signs of increased phospholipid turnover, electroretinograms of patients with schizophrenia are abnormal (suggesting low retinal DHA content) and incorporation of AA into phospholipids seems to occur with difficulty [2]. Taken together, these data suggest local AA depletion and insufficient synthesis of AA-derived eicosanoids, which becomes, e.g., noticeable by amelioration of psychiatric symptoms by fever-associated eicosanoid release, pain resistance by eicosanoid shortage at basal conditions and poor ability to exhibit an eicosanoid-induced flush upon nicotinic acid treatment. Das [115] hypothesized that perinatal supplementation of LCPUFA, especially EPA and DHA, may prevent schizophrenia in the adult. He considers schizophrenia to be a low-grade systemic inflammatory disease with origins in the perinatal period, probably triggered by maternal infection in a genetically susceptible individual that leads to excess production of proinflammatory cytokines both in the mother and fetus. The infection compromises LCPUFA status with devastating neurodevelopmental effects that should theoretically be favorably responsive to augmented LCPUFA status.

7. Fish oil, schizophrenia and depression

Low intake of the fish oil fatty acids EPA and DHA is implicated in the high incidence of depression in Western countries. The incidence of depression has increased markedly in recent decades [116], and there is a strong inverse correlation between national dietary fish intakes and rates of major and postpartum depressions [117,118]. Depressive symptoms are more likely to be encountered in infrequent fish consumers, and EPA and DHA status is low in depressive patients. There are also close relationships between fish consumption and the incidence of cardiovascular disease and depression, which fuelled the suggestion that depression should be included into the cluster of diseases that are associated with the metabolic syndrome [32]. Data from the United Kingdom show that the peak age of schizophrenia onset (i.e., 19–24 years) coincides with the highest intake of burgers (i.e., saturated fat) and full-sugar carbonated drinks and the lowest intake of oily fish [119]. A meta-analysis of dietary patterns in various countries linked the intake of refined sugar and dairy products to a worse 2-year outcome of schizophrenia, while a high national prevalence of depression became predicted from low intake of fish and seafood [120]. These data demonstrate that there are basically no differences between dietary risk factors for poor mental health, cardiovascular disease and some cancers. Five out of six double-blind, placebo-controlled trials with add-on omega 3 fatty acid (notably EPA) supplementation in schizophrenia have so far produced positive results, whereas 4 of 6 such trials produced positive effects in depression and bipolar disorders [32,37,121]. In other words, LCPUFAs are likely to be involved in the etiology of at least some psychiatric diseases, but also in their presentation in terms of severity at later age.

8. Conclusions

Current research on the etiology of psychiatric disease seems to fall short of the input of nutrition and may be somewhat overdosed with genetics and the traditional search for abnormal neurotransmitter metabolism per se. Folate, other one-carbon metabolite micronutrients, and dietary LCPUFA might play important roles in the etiology of at least some psychiatric diseases in their capacity as modulators of gene expression through epigenetic mechanisms (folate) and, as brain structural components, precursors of signal-transducing eicosanoids and ligands to nuclear transcription factors (LCPUFA). Low status of micronutrients involved in one-carbon metabolism and low LCPUFA status are also likely to be factors in psychiatric disease severity.

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