Ned Tijdschr Klin Chem Labgeneesk 2005; 30: 224-234

Nature or nurture in psychiatric disease

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This review seeks to find support for the hypothesis that (early) environmental factors, notably those of nutritional nature, play important roles in the etiology and severity of at least some psychiatric diseases. Complex diseases, like schizophrenia, autism and depression, do not inherit by Mendel's law, and the search for the underlying genetic basis has to this end been unsuccessful. Schizophrenia and autism relate to low birth weight and pregnancy complications, which predispose to developmental adaptations by 'programming'. Adaptation to the 'conditions of existence' occurs by mutation, epigenetics and interaction of the environment with transcription factors. Folate status, and one-carbon metabolism in general, is intimately involved in epigenetic modification, which refers to modifications of gene expression that do not entail a change of DNA base sequence. Studies in rats and hyperhomocysteinemic patients revealed that DNA methylation is sensitive to dietary folate and other factors in one-carbon metabolism. Early folate status of schizophrenic patients might be compromised as suggested by i) coinciding incidences of schizophrenia and neural tube defects (NTDs) in Dutch hunger winter cohorts, ii) coinciding seasonal fluctuations of birth incidence of patients with schizophrenia and NTDs, and iii) higher incidence of schizophrenia in methylene tetrahydrofolate dehydrogenase 677C→T homozygotes. Recent studies in both schizophrenia and autism point at epigenetic dysregulation by altered methylation of the investigated genes or chromosomal loci. Arachidonic acid (AA, from meat) and docosahexaenoic acid (from fish) are major structural components of brain phospholipids, as well as modulators of signal transduction and gene expression. Schizophrenic patients, and possibly autistic children, exhibit abnormalities in phospholipid metabolism that might cause local AA depletion and impaired eicosanoid-mediated signal transduction. There is a strong inverse relation between national fish intakes and rates of major and postpartum depressions. Four out of 5 randomized controlled trials with fish oil-derived eicosapentaenoic acid have so far produced positive results in schizophrenia, whereas 3/3 produced positive effects in depression and bipolar disorders. Patients with schizophrenia may also benefit from folic acid and fish oil supplements to lower their high risk of cardiovascular disease. It is concluded that folate, other one-carbon metabolite micronutrients, and LCP 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 (LCP). The nutrition-gut-brain axis in pregnancy and psychiatric patients is in urgent need of more attention.

Keywords: schizophrenia; autism; depression; folate; one-carbon metabolism; long chain polyunsaturated fatty acids; epigenetics

The stable cross-cultural and cross-racial incidence of schizophrenia, initially noticed by the 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 are likely to derive from the combination of a small number of affected 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 shows an increase that is unlikely to be explained by changes in diagnostic criteria or improvements in case ascertainment. It is e.g. estimated that in the past decades the prevalence

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in the USA exhibited a >10-fold increase, with <3 cases per 10,000 children in the 1970s to >30 per 10,000 in the 1990s (3).
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 and colon), we are dealing with a conflict between our contemporary lifestyle and our slowly adapting genome. This contribution summarizes the currently available data to support 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 (LCP) in the etiologies of schizophrenia and autism, and the role of dietary folate and LCP in patients with schizophrenia and depression.

Nature and nurture in the etiology of psychiatric disease

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, and 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 remark 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 developing to developed countries (5).
The high concordance of monozygotic (MZ) twins for schizophrenia (about 50%; (6)) and autism (60-90%; (7)) seem to argue in favor of the importance of genetic factors, since MZ twins are generally considered to have been exposed to the same (intrauterine) environment. Also DZ twins basically share the same environment, but the influence of genetic factors remains high even when corrected for concordance in dizygotic (DZ) twins (schizophrenia: 17%; autism: 0-10%). MZ twinning appears however to be an anomaly in itself, with an increased number of spontaneous abortions and structural congenital anomalies. Both MZ and DZ twins have growth rates that slow at 30 gestational weeks, which might 'program' (see below) them both developmentally and biochemically to different postnatal responses, compared with singletons (8). Moreover, MZ twins are either dichorionic (DC; about 33%) or monochorionic (MC; 67%) and the so-called twin-twin transfusion syndrome, due to placental anastomosis, affects MZ-MC twins in 7-30% of cases. At least MZ-DC and MZ-MC twins with the twin-twin transfusion syndrome do not share exactly the same intrauterine environments. There is evidence that schizophrenia concordance in MZ-DC twins amounts to only 10.7%, as compared to 60% concordance in MZ-MC twins (9). A case report of a discordant MZ twin for schizophrenia indicated that the birth weight of the affected twin was 1,620 g, as compared with 2,300 g for the unaffected counterpart (10). Simple MZ concordance rates may consequently overestimate schizophrenia heritability, with low birth weight and notably 'programming' probably being of more importance (9).

The influence of birth weight and pregnancy complications

Birth size has only a small genetic component and reflects mainly the quality of the intrauterine environment. 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' (11). 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, in which it is referred to as 'developmental plasticity' (12). It is considered to aim at adaptation of an individual to future environmental deprivation at postnatal life. The process of programming is not limited to an adverse environment in intrauterine life that stems from under or malnutrition, but may also derive from 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 or systems, including skeletal muscle, bone, kidney, liver and the cardiovascular, respiratory, endocrine, reproductive, central nervous and immune systems. Such adaptations may be beneficial for short-term survival but are in the long-term, stimulated by unfavorable postnatal lifestyle, implicated in some chronic non communicable diseases deriving from imperfections of e.g. endothelial function, glucose-insulin metabolism, insulin resistance and cholesterol metabolism. These imperfections are associated with adult diseases such as coronary artery disease, diabetes mellitus type 2, osteoporosis, the polycystic ovary syndrome and also schizophrenia (1, 13).
A recent study of perinatal risk factors for autism among 464 cases, 481 unaffected siblings and 1,311 controls in W-Australia, identified maternal age, threatened abortion during pregnancy and fetal distress as major risk factors, and found a positive relationship of autism severity (i.e. autism>pervasive developmental disorders not otherwise specified>Asperger) with the number and severity of perinatal complications. The obstetric complications of the unaffected siblings were more similar to cases than controls, which supported the conclusion 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 (14). In addition, a meta-analysis of prospective population-based studies (15) revealed that schizophrenia is associated with complications of

pregnancy (bleeding, diabetes, rhesus incompatibility, preeclampsia), abnormal fetal growth and development (low birth weight, congenital malformations, reduced head circumference), as well as to complications of delivery (uterine atony, asphyxia, emergency Cesarean section). Taken together, the available data suggest that birth weight and pregnancy complications might be important to the development of at least some psychiatric diseases, but the plausibility of causality would benefit greatly from the identification of the offending environmental factors and the elucidation of the underlying pathophysiological mechanism(s).

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 (16). The schizophrenia peak incidence in this cohort coincided with a 2.5 times higher incidence of neural tube defects (NTDs), which suggests the involvement of low folate status. Folate involvement was strengthened by the recent demonstration of coinciding seasonal fluctuations in birth incidence of patients with NTDs and schizophrenia, with both disorders exhibiting highest conception rates in May-June (17). In addition, a recent meta-study of 1,119 schizophrenia cases and 1,308 controls showed that the homozygous methylene tetrahydrofolate reductase (MTHFR) 677C→T variant is characterized by a 1.48 (1.18-1.86) higher odds ratio for schizophrenia, as compared with their CC and CT genotypes. 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 (18). Other arguments 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 (19) and the association of schizophrenia with the total number of siblings per household during childhood (20).

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 (21). Schizophrenia runs a more severe course in countries with a relatively high saturated fat intake and low unsaturated fat intake (2,22). In addition, serum folate concentrations correlate inversely with the severity of negative symptoms in schizophrenics (23) and a randomized controlled trial with methylfolate in patients with major depression or schizophrenia improved both clinical and social recovery (24). The picture emerges that low folate status, or possibly abnormal one-carbon metabolism in general, and low unsaturated fatty acid status are among the offending factors that are involved in both the etiology and the severity of at least some psychiatric diseases.

Folate, one-carbon metabolism and epigenetics

Epigenetics refers to modifications in gene expression that do not entail a change in DNA sequence. The discipline studies heritable, but potentially reversible, changes in gene expression by DNA methylation and/or alterations of chromatin structure (25-29). DNA methylation makes use of S-adenosylmethionine (SAM). 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 (figure 1). SAM-substrated DNA methylation by DNA methyltransferases is predominantly directed at CpG sequences, in which the cytosine is converted to 5-methylcytosine. 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 (30).

It is generally believed that epigenetic modifications are erased and reset during gametogenesis (i.e. meiosis), and therefore can not be transmitted to the next generation. This proved however not be the case for at least some mammalian genes. In other words, the epigenetic status of a gene can at least partially be transmitted to the offspring via 'imprinting', which leads to transgenerational inheritance of phenotypic characteristics through 'parent-of-origin specific effects'. In addition, 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 (28). These changes in the epigenome following mitosis, driven by (hormone initiated) developmental programs of cell and tissue differentiation, aging, microenvironment and stochastic fluctuations, may induce further variation in the ultimate phenotypic characteristics. Phenotypic adjustment by epigenetics, together with long-term adjustment of base-sequence by mutation and short-term adjustment by interaction of the environment with transcription factors, are at the center of our ability to adapt to the 'conditions of existence', which on its turn is the major driving force of evolution. Any change of environment beyond the flexibility of base-sequence, epigenetic modification, or the normal interaction with nuclear transcription factors puts us at risk of disease development.

Epigenetic deregulation of genes is more likely to be at the basis of complex diseases than gene mutations or polymorphisms. Epigenetics 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 (25, 29) the relation of complex diseases with low birth weight and obstetric complications (autism and schizophrenia), male/female 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 (28). Parent-of-origin imprinting and hormones are well known factors to affect epigenetic status but also

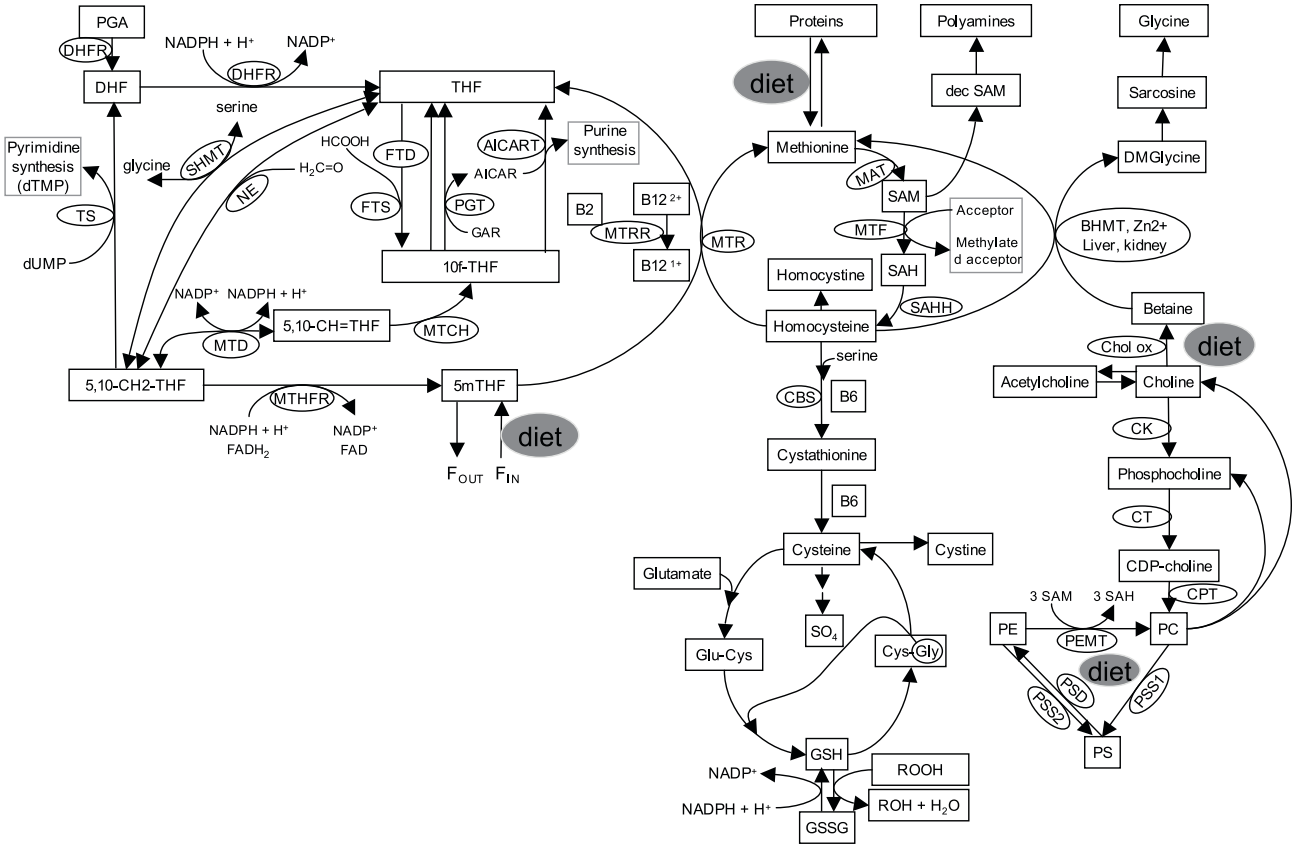

Figure 1. One-carbon metabolism and its immediately surrounding pathways. Indicated are the folate cycle (top, left), the methionine-homocysteine cycle (top, middle), the transsulphuration pathway and its connection with cystathionine/glutathione synthesis (middle, and middle-bottom), the betaine-homocysteine 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.

Abbreviations. 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); GSSG, oxidized glutathione; MAT, methionineadenosyltransferase; MTR, methionine synthase; MTCH, 5,10-methylenetetrahydrofolate cyclohydrolase; MTD, 5,10-methylenetetrahydrofolate dehydrogenase; MTF, methyltransferases (including DNA methyltransferases); MTHFR, 5,10-methylenetetrahydrofolate reductase; 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; SAH, S-adenosylhomocysteine; SAHH, S-adenosylhomocysteine hydrolase.

nutrition proved intimately involved in epigenetic status and its heritability. This was elegantly demonstrated by Waterland and Jirtle (31, 32), who studied the influence of 'methylation diets' on phenotype. They supplemented female mice with extra folic acid, vitamin B_{12}, choline and betaine (see figure 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 yellow 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 indicated the importance of homocysteïne and S-adenosylhomocysteine. Homocysteine and S-adenosylhomocysteine are products of SAM methylation (figure 1) and the latter is a potent inhibitor of methyltransferases. In this study Friso et al. (33, 34) showed that genomic DNA methylation correlates directly with folate status and inversely with levels of plasma homocysteïne. 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 (33). Their results suggest that interaction between nutritional status and genetic polymorphism has the potential to modulate gene expression through DNA methylation (33, 34). A recent study of Ingrosso et al. (35) with hyperhomocysteinemic patients on hemodialysis revealed global and locus-specific DNA hypomethylation, which was probably mediated by the associated increase of methyltransferase inhibitor S-adenosylhomocysteine. 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.

There is as yet no solid evidence of epigenetic factors in schizophrenia. The disease has, however, been linked to prenatal deficiencies of folate, vitamin B_6 and vitamin B_{12} (19), which are micronutrients that are either directly or indirectly involved in one-carbon metabolism and thereby in gene expression and repression through methylation (figure 1). Petronis et al. (36) 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 susceptibility to schizophrenia, and DRD2 antagonism is common to all antipsychotics. They studied two pairs of monozygotic 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 MZ co-twin, suggesting that schizophrenic patients have similar epigenetic status of DRD2. Several studies have shown low mRNA levels of the reelin gene in postmortem brains of patients with schizophrenia and bipolar disorders. The reelin protein is necessary for neuronal migration, axonal branching, synaptogenesis and cell signaling. A recent study confirmed low levels of the reelin protein and mRNA in postmortem brain of autistic patients, which together with some other anomalies suggested impairment of the reelin signaling pathway (37). Another recent study comprising 10 postmortem brains of schizophrenic patients and controls revealed promoter hypermethylation of the reelin gene, suggesting an epigenetic basis for the reelin gene hypoactivity in schizophrenia (38). James et al. (39) 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 (figure 1). In autism they found higher S-adenosylhomocysteine, adenosine and oxidized glutathione (GSSG) in conjunction with lower methionine, SAM, SAM/S-adenosylhomocysteine ratio, homocysteine, cystathionine, cysteine, total glutathione and total glutathione/GSSG ratio. This profile is consistent with lower methylation capacity (i.e. lower SAM/ S-adenosylhomocysteine 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. (40) 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.

Long chain polyunsaturated fatty acids and brain development

Low status of long chain polyunsaturated fatty acid (LCP; ≥20 carbon atoms and ≥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. LCP are either of the ω6 or ω3 series. Qualitatively and quantitatively important LCP are arachidonic (AA, an ω6LCP notably from meat) and eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids (both ω3LCP from fish) (41, 42). 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 (prostaglandins, thromboxanes, leukotrienes). LCP are building blocks of membrane phospholipids of all cells, in which they contribute to the physical properties of the membrane and (synaptic) signal transduction. EFA make up 20% of brain dry weight, including about 6% for AA and 8% for DHA. DHA and AA are determinants of membrane fluidity that is important for the efficacy of neurotransmitter-

receptor interaction and transporters, while AA is of special importance as a second messenger in signal transduction (43). DHA is the major structural lipid of the retinal photoreceptor outer segment membrane, where its fluidity is essential to sustain the extremely rapid conformational changes of rhodopsine (43, 44). Both AA and DHA are important to maintain a healthy endothelium of our cardiovascular system (45,46), of which the brain is obviously dependent for adequate nourishment. LCP 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 essential fatty acids to LCP. These abnormalities coincided with vascular dysfunction and persisted to adulthood (47).

LCP are not only important membrane structural elements, but, together with their eicosanoid products, they are also firmly implicated in gene expression. For example, dietary LCP are ligands to peroxisome proliferator activated receptors (PPARs) and suppress the expression of regulatory element binding proteins (SREBPs). 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 (48-51). 'Nutrigenomics' studies in rats revealed that ω3LCP (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 (52, 53). Dietary LCP 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 (54).

Fresh- and salt-water shoreline-based diets are likely to have been at the basis of our larger and more sophisticated brains than other primates. A constant dietary LCP supply and notably that of DHA might therefore be important, since we have limited ability to synthesize DHA from its essential fatty acid precursor alpha-linolenic acid (55-64). Higher dietary DHA intake may on its turn require higher AA intake to prevent competition between ω3LCP and ω6LCP, while alpha-linolenic acid has an independent role as a precursor to cholesterol synthesis in brain (65). This lays emphasis on a dietary ω3/ω6 balance (41, 42, 66, 67); 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 (67). Deficiency of ω3 fatty acids in primates is, amongst other conditions, associated with psychiatric pathology (68), and with reduced learning, abnormal electroretinograms and visual impairment in humans (69). AA and DHA status in preterm babies is related to birth weight, head circumference and length at birth (70-73), and AA and DHA may be protective against the central nervous, visual and auditory damage that is typical for (very) premature babies (74). Various studies have shown suboptimal neurodevelopment of both preterm and term babies receiving infant formulae without LCP, although many of these effects might be transient (75-79). It is clear that LCP have important functions in brain and that notably the low ω3LCP status of the contemporary Western diet might put us at risk of abnormal brain development.

The 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 incapable of producing the typical (prostaglandin-induced) cutaneous flush that follows nicotinic acid ingestion or topical application, and iiii) schizophrenia in developing countries with higher LCP intakes runs a less severe course (2, 21, 22). 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. 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 LCP, of which the intake has been subject to tremendous change since the industrial revolution. Lower contemporary intake 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 (80). It is possible that the genetic make-up of schizophrenic patients would in the past not have precipitated to disease and that the LCP-rich diet of our ancestors enabled them to take full evolutionary advantage of the associated intelligence and creativity.

Consistent with increased LCP losses, both patients with schizophrenia (22, 81) and autism (82) have increased activity of phospholipase A_2, which releases AA from membrane phospholipids (a process vital to brain cell signaling), while their LCP in erythrocytes seem to be more sensitive to oxidative stress *in vitro* (82, 83). Brain magnetic resonance spectroscopy studies in schizophrenics showed signs of increased phospholipid turnover, electroretinograms of schizophrenics 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 inability to exhibit an eicosanoid-induced flush upon nicotinic acid treatment. Das (84) hypothesized that perinatal supplementation of LCP, 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 pro-inflammatory cytokines both in the mother and fetus. The infection compromises LCP status with devastating neuro-developmental effects and should theoretically be favorably responsive to augmented LCP status.

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 (85) and there is a strong inverse correlation between national dietary fish intakes and rates of major and postpartum depressions (86, 87). 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 fed the suggestion that depression should be included into the cluster of diseases that carry features of the metabolic syndrome (22). Data from the UK show that the peak age of onset of schizophrenia (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 (88). 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 (89). These data demonstrate that there are no differences between dietary risk factors for poor mental health, cardiovascular disease and some cancers. Four out of 5 randomized controlled trials (RCT) with EPA supplements in schizophrenia have so far produced positive results, whereas 3/3 of such trials produced positive effects in depression and bipolar disorders (22, 90). In other words, LCP 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.

Comorbidity and the gut-brain axis of psychiatric patients

Life expectancy of schizophrenics is 20% shorter than the general population, and the excess mortality is for 60% attributable to physical illness (circulatory, respiratory, digestive and genitourinary disease) with the remainder on account of suicide (28%) and accidents (12%) (91). The newer atypical antipsychotic drugs have worrying effects such as weight gain, elevation of serum triglycerides and increased chance of diabetes mellitus type 2, which all constitute risk of cardiovascular disease in a population segment with little exercise, poor diet, almost universal smoking, and unhealthy lifestyle in general (22). In other words, patients with psychiatric diseases, especially schizophrenics, may benefit from good nutrition, and not merely with the aim of ameliorating psychiatric end points. Many studies of schizophrenic patients have shown low circulating folate and/or mildly increased homocysteine (23, 92-94) and (occasionally strongly) impaired LCP status, including that of ω3LCP (90, 95). Mild hyperhomocysteinemia (96, 97) and low ω3LCP status (98-100) are risk factors for cardiovascular disease events and death. Mild hyperhomocysteinemia is caused by low status of micronutrients involved in one-carbon metabolism, and folate, vitamin B_{12} (101) and betaine (102, 103) are among the principal determinants of plasma homocysteine concentrations in the general population. The strongly impaired LCP status as encountered in some of the studies of schizophrenic patients is probably due to *in vitro* artifacts and both the mild hyperhomocysteinemia and low LCP status may at least partially derive from smoking, poor dietary habits or unhealthy lifestyle in general. However, no matter the origin and whether these are features of all patients, both mild hyperhomocysteinemia and low ω3LCP status are correctable by supplementation of folic acid (or a folic acid, vitamin B_{12} and vitamin B_6 combination) and fish oil, which calls for patient-individual dietary counseling and dietary supportive care, if necessary.

The high incidence of gastrointestinal disturbances as found in autistic children by some investigators (104-106), but not all (107), deserves attention to prevent micronutrient deficiencies in at least those who have clear signs of these conditions. The relation with gluten and casein sensitivity in autism remains as yet unsolved, but there are too many anecdotic data from parents to put this subject aside. Thirty to 50% of autistic children have increased platelet serotonin (108), which stimulated many studies on a possible genetic background in the serotonin transporter. Also patients with carcinoid tumors have increased platelet serotonin, which derives from the release of serotonin by the tumor into the circulation, followed by its uptake in platelets. Platelet serotonin is consequently a sensitive test for the detection of serotonin-secreting carcinoid tumors, which constitute notably the 'functional' malignancies deriving from the mid-gut (109). Patients with diarrhea-predominant irritable bowel disease have higher mean platelet serotonin, with about 15% of them exhibiting above-reference values. Those exhibiting symptoms following consumption of a test meal showed increased post-prandial plasma serotonin, compared with those exhibiting no symptoms (110). These data reinforce the notion that platelet serotonin derives notably from neurotransmission processes in the gut, where approximately 80% of our body serotonin resides, and predict increased gut motility to be the most probable explanation for the above-normal platelet serotonin in a subgroup of autistic children.

Conclusions

Current research on the etiology of psychiatric disease seems to fall short of the input of nutrition and gastroenterology and may be somewhat overdosed with genetics and the traditional search for abnormal neurotransmitter metabolism *per se*. Folate, other one-carbon metabolite micronutrients, and LCP 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 (LCP). Low status of micronutrients involved in one-carbon metabolism and low LCP status are also likely to be factors in disease severity. Psychiatric patients might be at risk of even poorer diets and lifestyle than the general population and some of their drugs predispose to typically Western diseases. Increasing attention for the nutrition-gut-brain axis in psychiatric patients will hopefully change this picture in the near future.

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Samenvatting

Erfelijkheid of omgeving in psychiatrische ziekten. Muskiet FAJ. Ned Tijdschr Klin Chem Labgeneesk 2005; 30: 224-234

In dit overzichtsartikel wordt ondersteuning gezocht voor de hypothese dat (vroege) omgevingsfactoren, met name voeding, een belangrijke rol spelen in de etiologie en de ernst van tenminste enkele psychiatrische ziekten. Complexe ziekten, zoals schizofrenie, autisme en depressie, worden niet overgeërfd volgens de wet van Mendel, en de speurtocht naar de onderliggende genetische basis is tot dusver niet succesvol gebleken. Schizofrenie en autisme zijn geassocieerd met een laag geboortegewicht en zwangerschapcomplicaties, en deze predisponeren voor de aanpassing van de ontwikkeling door middel van 'programmering'. Aanpassing aan de 'leefomstandigheden' geschiedt door middel van mutatie, epigenetische modificatie en interactie tussen de omgeving en transcriptiefactoren. De folaatstatus, en het 1-koolstofmetabolisme in het algemeen, is nauw betrokken bij de epigenetica, hetgeen verwijst naar de modificatie van genexpressie die niet tot stand komt door een verandering in de DNA-basenvolgorde. Studies in ratten en in patiënten met hyperhomocysteïnemie hebben

laten zien dat de methylering van DNA gevoelig is voor het folaatgehalte van onze voeding en voor andere factoren in het 1-koolstofmetabolisme. De vroege folaatstatus van patiënten met schizofrenie is mogelijk gecompromitteerd, zoals gesuggereerd wordt door i) de samenvallende incidenties van schizofrenie en neuralebuisdefecten (NTDs) in Nederlandse hongerwintercohorten, ii) samenvallende seizoensfluctuaties in de geboorte-incidenties van patiënten met schizofrenie en NTDs, en iii) de hogere incidentie van schizofrenie in methyleentetrahydrofolaatdehydrogenase-677C→T-homozygoten. Recente studies in zowel patiënten met schizofrenie als autisme duiden op epigenetische disregulatie door middel van een veranderde methylering van de onderzochte genen of chromosomale loci. Arachidonzuur (AA, uit vlees) en docosahexaeenzuur (uit vis) zijn belangrijke structurele componenten van de fosfolipiden in onze hersenen, alsmede modulators van de signaaltransductie en de genexpressie. Patiënten met schizofrenie, en mogelijk autistische kinderen, vertonen abnormaliteiten in het fosfolipidenmetabolisme die een lokale AA-depletie en een verlaagde eicosanoïd-gemedieerde signaaltransductie kunnen veroorzaken. Er bestaat een sterke omgekeerde relatie tussen de nationale visinneming en de incidentie van depressie in engere zin en postpartumdepressie. Vier van de 5 gerandomiseerde gecontroleerde studies met het visolievetzuur eicosapentaeenzuur in patiënten met schizofrenie hebben tot dusver positieve resultaten laten zien, terwijl 3/3 studies effecten lieten zien bij depressie en bipolaire ziekten. Patiënten met schizofrenie kunnen ook baat hebben bij foliumzuur- en visoliesupplementen om hun hoge risico op hart- en vaatziekten te verlagen. De conclusie is dat folaat, andere micronutriënten in het 1-koolstofmetabolisme en LCP een belangrijke rol spelen in de etiologie van tenminste een aantal psychiatrische ziekten in hun functie als modulatoren van genexpressie via epigenetische mechanismen (folaat) en als structurele componenten van de hersenen, precursors van eicosanoiden en liganden van nucleaire transcriptiefactoren (LCP). Er is dringende behoefte aan meer aandacht voor de as tussen voeding, darm en de hersenen tijdens de zwangerschap en in psychiatrische patiënten.
Trefwoorden: schizofrenie; autisme, depressie; folaat; 1-koolstofmetabolisme; meervoudig onverzadigde langeketenvetzuren; epigenetica

Ned Tijdschr Klin Chem Labgeneesk 2005; 30: 234-237

Plantensterolen en voedingsvezels: trendsetters voor 'functionele voedingsmiddelen'

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'Functionele voedingsmiddelen' ('functional foods') zijn voedingsmiddelen waarin de aard of de beschikbaarheid van een component is gemodificeerd, of waaraan een component is toegevoegd, dan wel waaruit een component is verwijderd, door middel van (bio)technologische technieken. De consumptie van een dergelijke voeding kan leiden tot een verbeterde gezondheid of toestand van welbevinden en/of een verminderd risico op ziekte. Voorbeelden van functionele voedingsmiddelen om het LDL-cholesterol te verlagen zijn producten die verrijkt zijn met plantensterolen of plantenstanolen, of met de wateroplosbare vezel β-glucan. Deze stoffen verlagen de cholesterol- en/of galzoutopnname in de dunne darm. Geschat wordt dat het LDL-cholesterolgehalte met ca. 9% daalt bij een dagelijkse consumptie van 2 gram plantensterolen/stanolen. Deze reductie bedraagt ca. 6% bij een dagelijkse inname van 5 gram β-glucan.

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Trefwoorden: Functionele voedingsmiddelen; plantensterolen; plantenstanolen; voedingsvezel; β-glucan; LDL-cholesterol

De huidige voedingsrichtlijnen om het risico voor hart- en vaatziekten te verlagen zijn met name gericht op de reductie van het cholesterolgehalte in de atherogene LDL-deeltjes, of de reductie van de verhouding totaal cholesterol/HDL-cholesterol. Echter, ondanks strikte dieettrouw, zal het lipoproteïnenprofiel van een groot deel van de bevolking ongunstig blijven. Voor deze mensen bieden de zogenaamde 'functionele voedingsmiddelen' (functional foods) nieuwe mogelijkheden. Er is geen éénduidige definitie van een functioneel voedingsmiddel. Volgens Diplock et al. is het een voedingsmiddel, waarin door (bio)technologische technieken het gehalte van een bepaalde component is verhoogd, dan wel een voedingsmiddel waaraan een component is toegevoegd of waaruit een component is verwijderd (1). De consumptie hiervan heeft tot doel de gezondheid te behouden dan wel te bevorderen en/of zorgt voor een verlaging van het risico op bepaalde ziekten. Voorbeelden van functionele voedingsmiddelen die het LDL-cholesterol verlagen zijn margarines, yoghurt en melk die verrijkt zijn met plantensterolen of plantenstanolen, of muesli