Hypothesis

The glial growth factors deficiency and synaptic destabilization hypothesis of schizophrenia

Hans W Moises*1, Tomas Zoega2 and Irving I Gottesman3

Address: 1Molecular Genetics Laboratory, Department of Psychiatry, Kiel University Hospital, Niemannsweg 147, 24105 Kiel, Germany, 2Department of Psychiatry, National University of Iceland, Reykjavik, Iceland and 3Departments of Psychiatry and Psychology, University of Minnesota, Minneapolis, USA

E-mail: Hans W Moises* - moises@psychiatry.uni-kiel.de; Tomas Zoega - tomasz@landspitali.is; Irving I Gottesman - gotte003@umn.edu

*Corresponding author

Abstract

Background: A systems approach to understanding the etiology of schizophrenia requires a theory which is able to integrate genetic as well as neurodevelopmental factors.

Presentation of the hypothesis: Based on a co-localization of loci approach and a large amount of circumstantial evidence, we here propose that a functional deficiency of glial growth factors and of growth factors produced by glial cells are among the distal causes in the genotype-to-phenotype chain leading to the development of schizophrenia. These factors include neuregulin, insulin-like growth factor I, insulin, epidermal growth factor, neurotrophic growth factors, erbB receptors, phosphatidylinositol-3 kinase, growth arrest specific genes, neuritin, tumor necrosis factor alpha, glutamate, NMDA and cholinergic receptors. A genetically and epigenetically determined low baseline of glial growth factor signaling and synaptic strength is expected to increase the vulnerability for additional reductions (e.g., by viruses such as HHV-6 and JC virus infecting glial cells). This should lead to a weakening of the positive feedback loop between the presynaptic neuron and its targets, and below a certain threshold to synaptic destabilization and schizophrenia.

Testing the hypothesis: Supported by informed conjectures and empirical facts, the hypothesis makes an attractive case for a large number of further investigations.

Implications of the hypothesis: The hypothesis suggests glial cells as the locus of the genes-environment interactions in schizophrenia, with glial asthenia as an important factor for the genetic liability to the disorder, and an increase of prolactin and/or insulin as possible working mechanisms of traditional and atypical neuroleptic treatments.

Background

The current understanding of the origin of schizophrenia is mainly based on the multifactorial-threshold (MFT) model of genetic liability and the neurodevelopmental model [1]. The former is supported by family, twin, adoption and modeling studies [2–4], and the latter by circumstantial evidence from clinical, epidemiological, neuropathological, and imaging studies [5,6]. Growth deviations found in many cases of schizophrenia support the neurodevelopmental hypothesis, e.g., low birth weight, late maturation, leptosomatic body build, large ventricles and low brain volume [5–8]). Neuronal growth
and development [9,10] is controlled by growth factors synthesized by glial cells [11]. Glial cell loss [12], decreased expression levels of glia-related genes [13], and increased levels of S100B [14,15], a marker of glia cell integrity, has been observed in schizophrenia suggesting a role for glial growth factors in the pathogenesis of the disorder.

Genome scans in schizophrenia have converged on several chromosomal locations [16]. A convergent loci approach has been proposed in the Proceedings of the National Academy of Science USA as a technique for discovering the molecular basis for a disease [17]. Convergent techniques such as the convergent loci (CL) or the convergent functional genomics approach [16,18,19] search for agreement between the chromosomal position of susceptibility genes for the disease and the function of the genes discovered at that position. In convergent approaches, the function of the genes is usually defined as evidence for their involvement in the disorder, derived from non-linkage studies such as gene expression analyses [16,18,19] or from evidence-based hypotheses such as the neurodevelopmental hypothesis of schizophrenia. Because of the essential role of the GGF neuregulin for neurodevelopment [20,21], we applied the CL approach to schizophrenia linkage data and GGFs-related genes. In our view, convergent techniques do not prove the existence of a causal relationship. However, they are useful

**Figure 1**

**Pooled linkage results in schizophrenia and localization of genes related to glial growth factors and synaptic strength.** Data compiled from 60 published (not abstracts) linkage studies in schizophrenia (including two studies using endophenotypes of the disorder) [73,74,146–203]. Each dot represents evidence for linkage obtained in an independent sample. The level of significance is shown according to the criteria of Lander and Kruglyak [204]. Red indicates significant (lod score = 3.6), yellow suggestive (lod score = 2.2) evidence and white hints (p ≤ 0.05) for linkage. Only the marker showing the best evidence for linkage in the region were used from each study. Markers within a distance of 20 Megabases (Mb) are displayed at the same chromosomal position. The distance between linkage marker and gene in Mb is given below the gene. Chromosomal positions were obtained from the Unified Database for Human Genome Mapping (UDB) [205] and the UCSC Human Genome Project Working Draft. [http://genome.ucsc.edu]. A susceptibility gene within a distance of 20 Mb from a genetic marker can be detected by linkage analysis. The marker-gene distances range from 0.1 to 19.1 (median 1.7) Mb.
tools for the generation and preliminary testing of causal hypotheses.

The GGFs deficiency hypothesis is part of the broader working hypothesis of a decrease in the cerebral protein-synthesis rate (CPRS) developed by one of us (HWM) as result of his attempt to find a common denominator for the diverse results of schizophrenia research [7]. The evolutionary approach employed in the latter investigation suggested that neuregulin 1 (NRG1) might be one of the susceptibility genes for schizophrenia (Figure 1 in [7]) motivating further theoretical and experimental investigations. The hypothesis presented here provides a heuristic explanation for the neurodevelopmental and genetic findings in schizophrenia.

The function of glia and its growth factors

Glial cells play important roles in the developing [11] as well as in the adult central nervous system (CNS). In the adult CNS, glia has a supportive, a protective, a regenerative, and an active regulatory role. Glia cells are sensors of infection and produce cytokines to limit viral replication. In adults, they induce neurogenesis in the hippocampus and the subventricular zone [22]. influence neuronal activity and synaptic strength [23], and appear to be the third partner in synaptic transmission (tripartite synapse) [24]. Synaptic strength and cellular growth depend on the synaptic and the general protein-synthesis rate [25,26] which is influenced by growth factors such as neurotrophins and neuregulins [27,28]. Glial cells are part of a positive feedback loop between presynaptic neurons and their postsynaptic targets [29] involving neurotrophins and neuregulins (NRGs).

NRGs are synthesized by neurons [11] and promote the differentiation, survival and repair of the neuronal targets such as glial cells [11], acetylcholine receptors [21], and postsynaptic densities (PSD) in hippocampal neurons [30]. Neuregulin-1 (NRG1) is concentrated at synaptic sites suggesting a role in synapse-specific gene expression [28]. Furthermore, NRGs influence the growth of neural precursor cells, the radial migration of newborn neurons during neocortex genesis, the rate of migration in a dose-dependent manner [31], the interaction between pre- and postsynaptic neurons during synaptogenesis including neuromuscular synapse, activity-dependent maintenance of synaptic connections, synaptic plasticity, long-term potentiation, and the expression of ligand and voltage-gated channels in central neurons [9,11,20,21,32–34]. NRGs are also known as glial growth factor (GGF), Neu differentiation factor (NDF), heregulin, sensory and motor neuron derived factor (SMDF), and acetylcholine receptor inducing activity (ARIA) [21].

Biochemically, NRGs are structurally related to what is perhaps the best studied trophic factor – epidermal growth factor (EGF) [11] and encode a large group of polypeptide growth, survival and differentiation factors [20,21] that all contain an extracellular epidermal growth factor (EGF)-like domain, which is essential for their bioactivity [35]. They are derived by alternative splicing from four genes: NRG1, NRG2 also known as Don-1 and NTAK, NRG3, and NRG4. NRG1-3 is expressed during neurodevelopment and in the adult CNS [21], whereas NRG4 transcripts have not been detected in neural tissue [21]. The cytoplasmic tail of NRG interacts with the protein kinase LIM kinase 1 (LIMK1) [36].

NRGs act through a network of ErbB tyrosine kinase receptors consisting of ErbB1 (also termed EGF receptor or HER1), ErbB2 (Neu/HER2), ErbB3 (HER3) and ErbB4 (HER4) [11,20,21,37]. NRGs bind to ErbB2-4, EGF and transforming-growth factor alpha (TGFα) to ErbB1 [21,37]. ErbB receptors serve as docking sites for cytoplasmic signaling molecules such as Grb2-related adaptor protein 2 and phosphatidylinositol-3 kinase (PI3K) [21,37]. In addition, the ErbB receptor system integrates signaling events from other receptor classes, such as G-protein-coupled receptors and cytokine receptors [37].

NRGs induce the expression of growth factors, cholinergic, GABAergic and glutaminergic receptors (e.g., transforming growth factor beta [21], N-methyl D-aspartate (NMDA) receptor 2C subunit [21], gamma-aminobutyric acid (GABA) receptor beta-2 subunit [21], acetylcholine receptor (AchR) alpha-5, alpha-7 [38], beta-4, delta and epsilon subunits [21,39]. The promoter region of the nicotinic AchR epsilon subunit gene contains a NRG-responsive element [39]. Furthermore, the NRG-dependent regulation of AChRs at the neuromuscular junction (NMJ) requires the serine/threonine cyclin-dependent kinase 5 regulatory subunit 1 (p35) [21].

NRGs appear to act synergistically with other growth factors such as insulin-like growth factor-1 (IGF1) [40,41], EGF [42], insulin [43], and growth arrest specific genes (GAS6) [44–46]. In turn, neurotrophic growth factors (e.g., BDNF and NT-3), glutamate, and neural activity increase the expression of NRG [34,47] and of neuitin in hippocampal and cortical neurons, regions well characterized in regard to synaptic plasticity [48].

With regard to the latter, ErbB receptors are enriched in postsynaptic densities (PSD) and interact with other PSD proteins such beta-2 syntrophin, NMDA receptor subunit 2C and 2B, Ca2+-activated potassium channels [21,49,50], protein kinase C interacting protein (PICK1) and glutamate (AMPA subtype) receptors [21].
The synaptic connections are maintained by a positive feedback loop between the presynaptic neuron and its targets which includes glial cells. The latter provide neurotrophins, e.g., GDNF, BDNF, NT-3, NT-4, hepatocyte growth factor [11,34] that enhance neuronal survival, differentiation, plasticity, pruning, synaptic strength and stabilization, synaptic transmission, presynaptically by increased secretion of neurotransmitters and postsynaptically via NMDA receptors [9,11,51,52]. The synthesis of neurotrophins is down regulated by inhibitory synaptic activity (e.g., GABA), up regulated by neuregulin, activation of metabotropic glutamate group I receptors (mGlur1), acetylcholine, physical exercise, physical and social stress, cytokines, and neurotrophin itself [9,52–55]. Neurotrophins are in short supply in the CNS [9]. Neurons and axons that do not receive adequate amounts of neurotrophic factors risk degeneration or synapse elimination [9]. Neurotrophins are critical for long-term potentiation (LTP) in the hippocampus and activity-dependent synaptic plasticity (SP), which are thought to be cellular models for learning and memory [52].

GGFs such as NRG1, NGF, and EGF induce protein-synthesis [56,57], which is required for cellular growth [25], for activity-dependent maintenance of synaptic connections [58], synaptic strength [26], and long-term memory [59].

**Convergent loci**

A search for convergent loci revealed 41 genes (see Fig. 1) with related functions localized within significant or potential linkage regions of schizophrenia (chromosomal localization in parenthesis): neuregulin-1 (NRG1) (8), neuregulin-2 (NRG2) (5), neuregulin-3 (NRG3) (10), epidermal growth factor (EGF) (4), and neuregulin receptor ErbB3 (12), transforming-growth factor alpha (TGFα) (2), transforming-growth factor beta receptor II (TGFBR2) (3), LIMK1 (7), Grb2-related adaptor protein 2 (22), phosphoinositide-3 kinase class 2 beta polypeptide (PIK3C2B) (1), GABA receptor beta 2 (GABRB2) (5), acetylcholine receptor alpha 7 (CHRA7) (15) and epsilon (CHRNE) (17), growth factors such as glial cell line derived neurotrophic factor (GDNF) (5), GDNF receptor alpha 1 (GFRA1) (10), GFRA2 (8), GFRA4 (20), GDNF family related persephin (19), glutamate and its receptors (GRM1, metabotropic glutamate receptor 1) (6), GRM4 (6) GRM5 (11) and GRM6 (5), insulin-like growth factor I (IGF1) (12), insulin receptor (INSR) (19), insulin receptor substrate 1 (IRS1) (2), GAS6 (13) and GASS5 (1), neurtin (6), syntrophin B2 (16), protein kinase C interacting protein (PIPK1) (22), NMDA receptor 2B (12) and 2 C (17), p35 (CDK5R1) (17). Furthermore, epiregulin (4) is a potent pan-ErbB ligand [60]. Ephrins such as ephrin-B2 (13) and ephrin-A5 (5) are involved in neurodevelopment, and in the adult CNS in LTP, synaptic strength [61], and cell proliferation of the adult subventricular zone [62]. Fibroblast growth factors such as FGF2 (4) and indirectly the FGF binding protein 1 (FGFBP1) (4) have a similar effect on development, adult neurogenesis, cell survival and synaptic transmission [63,64]. Cytokines are neurotoxic or neurotrophic [65]. For example, interleukin-8 (IL8) (4) exerts neurotrophic effects on glial cells [65] and the latter constitutively release tumor necrosis factor alpha (TNF) (6), another cytokine, which markedly influences synaptic strength [66] and leads to impaired insulin signaling via ErbB2 and ErbB3 [67]. Moreover, interleukin-1 receptor accessory protein-like 1 (X), a member of the IL1 receptor family, is highly expressed in the adult hippocampus suggesting a role in learning, memory, and synaptic strength [68]. Neurogranin (11) is concentrated in the post-synaptic terminals of the hippocampus and involved in learning, LTP, and synaptic plasticity [69].

The convergent loci of the genes described above are displayed in Fig. 1 along with genetic markers showing some evidence for linkage in schizophrenia. The inclusion of significant as well as non-significant linkage markers may well be the object of criticism if the intention were to prove, rather than to generate in the context of discovery, a hypothesis which has to be tested by other research programs. The convergences shown in Fig. 1 led us to propose the following hypothesis for schizophrenia.

**Presentation of the hypothesis**

The growth factors deficiency and synaptic destabilization hypothesis of schizophrenia (GGF/SD) states that a functional deficiency of glial growth factors and of growth factors produced by glial cells such as neurotrophins and glutamate (termed here GGFs) leading to a weakening of the synaptic strength may be implicated as one of the important causes of schizophrenia (see Fig. 2).

The hypothesis suggests that glial cells might be the locus of the genes-environment interactions in schizophrenia. A genetically and epigenetically determined low glial growth factor signaling and baseline synaptic strength are expected to increase the vulnerability for additional reductions and for developing schizophrenia.

GGFs are part of a positive feedback mechanism for the stabilization of synaptic connections. The baseline strength or weakness of the synaptic connections is assumed to be normally distributed in the general population and to be influenced by factors relevant for growth, that is by environmental as well as by genetic factors. Individuals with a genetically and/or epigenetically determined weaker synaptic feedback mechanism display differences in growth rate, brain development, maturational, metabolism, personality, cognition, memory, risk for neurodevelopmental disturbances and for schizophre-
nia. A decrease of GGFs (e.g., at the end of brain growth and at the beginning of menopause) might lead to the negative symptoms observed in schizophrenia prodromes [70,71].

The reduction of the synaptic strength below a certain threshold is postulated to cause synaptic destabilization and acute schizophrenic symptoms. Such a reduction might result from specific genes, from the genetic background (e.g., anabolic hormones and general protein-synthesis rate) or from environmental factors such as reduced brain activity [34,47], neurotoxins or virus infections of glial cells. An acute and pronounced deficiency of GGFs causes axon withdrawal followed by regeneration and synaptic remodelling. The probably incomplete regeneration in individuals with a decreased functional activity of GGFs might be responsible for the incomplete remissions observed in schizophrenia.

Testing the hypothesis
Does the GGF/SD hypothesis fulfill the fundamental conditions for a scientific hypothesis [72]: explanatory power and testability?

Explanatory power
A scientifically useful hypothesis should explain the main facts and be, at least, consistent with the rest of the facts [72]. The GGF/SD hypothesis is able to explain major findings of schizophrenia research such as (1) genetic linkage, (2) neurodevelopmental disturbances, deviant neuronal migration, (3) prenatal timing, (4) expression studies, (5) multiorgan involvement, (6) growth deviations, (7) seasonality of birth, (8) age of onset, (9) neurodegeneration, (9) regeneration and neural remodelling, (11) memory disturbances, and (12) the maintenance of the disorder in the population despite the reduced fertility of the patients.

(1) Genetic linkage: The CHRNA7 gene on chromosome 15q shows evidence for linkage to schizophrenia [73,74] and appears to be downstream of NRG because NRG leads to an increase of alpha7 nicotinic acetylcholine receptors (CHRNA7) and is highly expressed in cholinergic neurons of the CNS [38]. The NRG1 gene itself is located within a linkage region of schizophrenia on 8p. Further convergences seem to exist (see Fig. 1). Moreover, reported associations of schizophrenia with 5-HT receptor 2A [75], 5-HT5A [76], NT-3 [77], metabotropic glutamate receptor subtype 5 [78], NOOTCH4 [79], possibly NRG1 [80], potassium channel gene hKCa3 [81], proline dehydrogenase (oxidase) PRODH2 [82,83], and regulator of G-protein signaling 4 (RGS4) [8,84] are all in agreement with the hypothesis. NRG1 is a glial growth factor which interacts with Ca2+-activated potassium channels [21,49,50]. Notch plays a role in gliogenesis [85]. NT-3 is produced by glial cells [11,34], 5-HT increases the release of glial glutamate [86]. Proline oxidase appears to catalyze the first step of an alternative route for glutamate production in glial cells of the hippocampus [87]. The receptors for EGF and neuregulins, the ErbB receptor system, integrates also the signal transduction from G-protein-coupled receptors [37], which is inhibited by RGS4 [88]. However, some of the findings cited in this paragraph and shown in Fig. 1 are very probably false positives.

(2) Neurodevelopment: evidence for glial cell abnormalities, neurodevelopmental disturbances, neuronal migration, and cognitive disturbances has been found in schizophrenia [6,12,13]. Glial cells play an important role
in neurodevelopment and neuronal migration [11,89], and the highest ratio of glia-to-neurons is found in the neocortex suggesting a key role for glial cells in higher cognitive functions [90].

(3) Prenatal timing: NRG is important for midgestation [20,21], a prenatal period with evidence for neurodevelopmental disturbances in schizophrenia [6].

(4) Expression studies in postmortem brains are also in line with the postulated functional deficiency of GGFs. Since GGFs are involved in growth, they should influence the expression of many genes. Indeed, a large number of decreased mRNAs or proteins has been reported in schizophrenia (for review [7], e.g., synapsin, synaptophysin, glutamate receptors, somatostatin, glutamic acid decarboxylase, protein kinase C, adenylate cyclase, regulator of G-protein signaling 4 (RGS4) [19], MAP kinase phosphatase MKP2, postsynaptic density protein 95 growth associated protein-43, and alpha7-nicotinic receptor [91]). A functional GGFs deficiency could also explain the results of a gene expression analysis suggesting a glial cell deficiency in schizophrenia [13].

(5) Multiorgan involvement has been observed in schizophrenia, e.g., brain, blood vessels (nailfold plexus), lung (cancer, TBC), immune system (lymphocytes, rheumatoid arthritis), and skin (dermatoglyphics) (for review [7]). These findings are in line with the expression of NRG in neurons, glia, heart, liver, stomach, lung, kidney, immune system, and skin [11,20], of GAS6 in an equal number of tissues including rheumatoid arthritis [92], and finally with the role of the ErbB receptors in growth regulation in a wide variety of cell types [20].

(6) Growth deviations have been observed in schizophrenia [5–8]. NRGs are growth factors and act synergistically on glial cells with the insulin-like growth factor I (IGF1) [93], a major determinant of fetal growth [94] as well as with GAS6, which is involved in bone formation and glial growth [44,95]. In addition, the reported negative association between schizophrenia and cancer [96,97] agrees with the role of ErbB receptors in the genesis of carcinomas [20].

(7) Seasonality of birth: The increase of IGF1 in the summer [94] might account for the seasonality of birth in schizophrenia [98]. IGF2 is imprinted in humans [99,100]. Imprinted genes often help to regulate the growth of the fetus [101]. Growth regulatory signals lead to histone acetylation and hence epigenetic variation of gene expression [102].

(8) Age of onset: Brain growth might be used as an indirect indicator of the activity of GGFs. Fig. 3 shows that a decrease in head and brain growth is accompanied by a sharp increase in the risk for developing schizophrenia.

(9) Neurodegeneration: Disruption of the NRG1 gene causes neuronal degeneration after initial synapse formation, especially in motor neurons, [33,103]. Degeneration of the second motor neuron does also take place in schizophrenia causing atrophy of skeletal muscle fibres, a mechanism elucidated by Meltzer in the search for the cause of increased serum CK, a muscle-derived enzyme, in acute psychosis [104,105]. Furthermore, a GGFs deficiency would explain the increased levels of S100B, a marker of glial cell integrity, in acute schizophrenia [14,15] and the evidence for a minor neurodegenerative process in chronic schizophrenic patients revealed by longitudinal MRI studies [106].

(10) Regeneration: NRG is important for neuronal regeneration following environmental insults [21]. A genetically or epigenetically determined deficiency of GGFs is compatible with the limited regeneration of motor neurons observed in schizophrenia [104,105] and with the incomplete remission of the disorder, which is the foundation of Kraepelin’s schizophrenia (dementia praecox) concept.

(11) Memory disturbances: In the adult brain, NRGs and neurotrophins appear to be involved in activity-dependent synaptic plasticity [30,48,51,107], a mechanism rele-
vant to protein-synthesis dependent long-term memory [59]. They are expressed in brain regions well characterized in regard to synaptic plasticity (hippocampus and cortex). Memory impairment has been found in schizophrenia and appears to be responsible for the characteristic symptoms of the disorder [108].

(12) The maintenance of schizophrenia in the population despite the reduced fertility of the patients [109] is a partially unsolved puzzle [110] which might be explained by the postulated growth deficiency. Growth-dependent birth weight is the classical example for stabilizing selection in humans [111], a selection against both extremes.

We conclude that the postulated GGFs deficiency and synaptic destabilization in schizophrenia fulfills the first requisite for a scientific hypothesis, to explain the main facts. However, is the hypothesis also consistent with the rest of the facts? For such a test, an extensive list of 84 major findings of schizophrenia research has been compiled by one of us (HWM) from the literature using books and review articles for literature from 1900 to 1975, PubMed’s and PsycLit’s electronic databases for publications from 1966 to 2001 and from 1974 to 2001, respectively [7]. A major finding was defined operationally as results obtained by at least two independent groups of researchers. The GGF/SD hypothesis appears to be consistent with the major findings in schizophrenia.

Testability
The second fundamental condition for a scientific hypothesis is to be susceptible to verification and refutation and to aid in the prediction of new facts and relationships [72].

The GGF/SD hypothesis can be verified or falsified by searching for concomitant variations between the postulated independent and the dependent variables, that is between concentration or signal transduction of GGFs such as NRG, IGF1, GAS6, TNF-alpha, neuritin etc. and schizophrenia or schizophrenia-like symptoms. The independent variables can be measured in animals or humans, and the dependent variable in animal models of the disease endophenotypes or in acute schizophrenic psychosis, preferably with elevated serum CK or S100B. The different parameters of GGFs can be investigated at different levels and by different methods, e.g., by studying mRNA, proteins or signal transduction and by using knock-out animals, antisense mRNA, cDNA microarrays, antibodies or signal transduction assays in immune cells, fibroblasts or muscle cells from patients. A confounding variable might be the large number of alternatively spliced NRGs.

Furthermore, deductive reasoning from the hypothesis leads to certain logical consequences that can be tested. The hypothesis predictions include, among others, (1) a reduction of neurotrophins and synaptic strength induced by virus infections of glial cells, (2) the involvement of risk genes for schizophrenia in the pathway of GGFs and/or synaptic strength (SS), (3) differences in the structure and function of organs influenced by NRG, (4) a decreased synaptic protein-synthesis rate, decreased SS, and synaptic destabilization as a common final pathway, and (5) synaptic stabilization via improvement of astrogia function as an antipsychotic drug mechanism.

(1) The predicted reduction of neurotrophins/SS by acute, latent, or reactivated virus infections can be investigated in animal models or glial cell cultures. Glial cells display genetically determined individual differences to virus infections [112] and are infected by a large number of viruses (for review [113,114]). Especially interesting in this regard is the human herpes virus-6 (HHV-6) and the JC virus (JCV). The HHV-6 infects worldwide, within the first two years of life, nearly 100% of the human population, infects predominantly glial cells with a low-level of viral production [115], persists latently lifelong, and has been detected in 13% – 74% of normal human brains [116–118]. The JCV infects more than 70% of the world’s population during early childhood [119], infects mainly glial cells (oligodendrocytes as well as astrocytes) [114,120], remains in the latent state without apparent clinical symptoms but shows in vitro the ability to deregulate the cellular function of oligodendrocytes and perhaps astrocytes [121,122]. The JC virus is spread by urban sewage [119,123] which might contribute to the urban factor observed in schizophrenia (for review [8]).

(2) Another prediction is that some of the GGF- and SS-related genes increase the risk for schizophrenia. Such genes (e.g., Fig. 1) can be tested for allelic association (linkage disequilibrium, LD) with schizophrenia. Since LD studies in complex disorders have often identified regulatory regions influencing the disease [124], and since different parts of the same gene are not necessarily in LD with each other (e.g., [125]), candidate genes for schizophrenia and their regulatory regions will have to be investigated by haplotypes consisting of densely spaced SNPs. Under optimal circumstances, sample sizes of more than 500 affected appear to be required to detect LD in complex disorders such as schizophrenia [126,127]. Optimal circumstances are present, when a single disease-causing mutation accounts for a large proportion of the phenotypic variance and has arisen recently on a relatively uncommon haplotype background [128]. Such favorable circumstances rarely exist in schizophrenia. Locus and allelic heterogeneity are common in complex disorders, produce dramatic decreases in power [128], and an increase in sample size (e.g., [129] or by meta-analysis [130]) further increases heterogeneity [124]. Therefore,
the frequent elusiveness of positional cloning results in complex disorders is hardly surprising [124,131]. Given the inefficiency of LD studies [124,132] and the generally low repeatability of positive findings in complex disorders [127], negative results of LD studies are, unfortunately, unable to disprove anything. To falsify the hypothesis, it might be necessary to investigate protein concentrations and to perform functional assays of cells derived from schizophrenic patients and their relatives.

(3) The multiorgan expression of GGFs such as NRG, GAS6 and their receptors predicts differences in the structure and function of relevant organs such as liver, skin, heart, lung, kidney, bones, muscle, sensory and motor neurons, and acetylcholine receptor density at the NMI. For example, a decrease of muscle mass, of muscular-growth rate, of bone structure, and an increase of the risk for liver cirrhosis are predicted for schizophrenic patients, their family members and for introversion, an associated personality trait [7].

(4) A decreased rate of glial, neuronal or synaptic protein synthesis is predicted by the GGF/SD hypothesis based on the facts that NRGs, GAS6, and other GGFs are growth factors, that NRGs result in an increased synthesis of growth factors, that growth is associated with protein synthesis, and that NRG1 stimulates the protein-synthesis rate [7,56].

(5) Finally, the GGF/SD hypothesis predicts an antipsychotic effect by reducing the synaptic destabilization via the improvement of astroglial function. The prediction can be tested by stimulation of the synaptic protein synthesis rate, e.g., via glial growth factors such as NRGs, neurotrophins, EGF, IGF1, insulin, prolactin, activation of ErbB receptors or PI3K. Hyperprolactinemia via dopamine receptor blockade is a well known "side-effect" of traditional neuroleptics [133]. Dopamine receptor blockade and/or elevation of prolactin levels have also been reported for atypical antipsychotics such as clozapine [133], olanzapine [133], risperdone [134], amisulpride [135,136], ziprasidone [137], and zotepine [138]. Furthermore, clozapine and olanzapine increase the level of insulin [139–141]. This suggests that an increase of prolactin and/or insulin might be the working mechanism of neuroleptics. Hence, an augmentation of antipsychotic efficacy is predicted by combining neuroleptics with a predominant insulin profile with others showing a marked hyperprolactinemia. The latter prediction can be easily tested, e.g., by combining clozapine or olanzapine with amisulpride in the treatment of acute schizophrenic psychosis.

Implications of the hypothesis

A major weakness of the hypothesis outlined above is that it is based on circumstantial evidence. However, "the hypothesis is the principal intellectual instrument in research" [72] and it is an "utterly misleading view that knowledge can be advanced by merely collecting facts" [209]. An advantage of the present hypothesis is that it not only fulfills the two fundamental conditions for a useful scientific hypothesis – explanatory power and testability – but that it also provides a unifying explanation for several diverse findings in schizophrenia. Furthermore, it is in agreement with other hypotheses, e.g., the polygenic [2], epigenetic [142], virus [143], nicotinergic [91], glutamate [144,145], synaptic plasticity, cerebral protein-synthesis rate [7], and neurodevelopmental hypotheses [5,6,8]. If the hypothesis of synaptic destabilization by a functional deficiency of pathways involved in GGFs is eventually proven by a comprehensive research program, it will provide a path for the rational design of preventive and therapeutic interventions.

Competing interests

None declared.

Abbreviations

AchR, acetylcholine receptor; ARIA, acetylcholine receptor inducing activity, a NRG; BDNF, brain-derived neurotrophic factor; Cl, convergent loci; CHRNA7, alpha7 nicotinic acetylcholine receptors; CK, creatine phosphokinase; CNS, central nervous system; EGF, epidermal growth factor; GABA, gamma-amino butyric acid; GAS6, growth arrest specific gene 6; GDNF, glial-derived neurotrophic factor; GGF, glial growth factor, a NRG; 5-HT, 5-hydroxytryptamine, serotonin; IGF1, insulin-like growth factor-I; INS, insulin receptor; JCV, JC virus; Mb, Megabases; MFT, multifactorial-threshold; NDF, Neu differentiation factor, a NRG; SNPs, single-nucleotide polymorphisms; SP, synaptic plasticity; SS, synaptic strength and stability; TGFA, transforming-growth factor alpha; TNF, tumor-necrosis factor alpha.

Note added at proof

After the manuscript had been accepted, Kendler and co-workers reported an interesting finding which is in agreement with the synaptic destabilization hypothesis presented here, an allelic association between the human dysbindin gene DTNBP1 and schizophrenia. According to the authors, the dysbindin gene seems to influence the synaptic function. See, RE Straub et al. Genetic Variation
in the 6p22.3 Gene DTNB1P, the human Ortholog of the mouse Dysbindin, is Associated with Schizophrenia. Am J Hum Genet 2002 Jul 3;71 (2). [http://genomebiology.com/resolver.asp?PubMedID=12098102]

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