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Cytokine hypothesis of schizophrenia pathogenesis: Evidence from human studies and animal models

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Abstract
The pathogenesis of schizophrenia remains to be fully characterized. Gene-environment interactions have been found to play a crucial role in the vulnerability to this disease. Among various environmental factors, inflammatory immune processes have been most clearly implicated in the etiology and pathology of schizophrenia. Cytokines, regulators of immune/inflammatory reactions and brain development, emerge as part of a common pathway of genetic and environmental components of schizophrenia. Maternal infection, obstetric complications, neonatal hypoxia and brain injury all recruit cytokines to mediate inflammatory processes. Abnormal expression levels of specific cytokines such as epidermal growth factor (EGF), interleukins (ILs) and neuregulin-1 (NRG-1) are found both in the brain and peripheral blood of patients with schizophrenia. Accordingly, cytokines have been proposed to transmit peripheral immune/inflammatory signals to immature brain tissue through the developing blood-brain barrier, perturbing structural and phenotypic development of the brain. This cytokine hypothesis of schizophrenia is also supported by modeling experiments in animals. Animals treated with specific cytokines of EGF, IL-1, IL-6, and NRG-1 as embryos or neonates exhibit schizophrenia-like behavioral abnormalities after puberty, some of which are ameliorated by treatment with antipsychotics. In this review, we discuss the neurobiological mechanisms underlying schizophrenia and novel antipsychotic candidates based on the cytokine hypothesis.

INTRODUCTION

Schizophrenia has been one of the most puzzling mental disorders since it was first categorized as dementia praecox almost 100 years ago. Extensive investigation over many decades has led to the proposal of a model of disease causation based on gene-environmental interaction.[1] Recent genetic studies have repeatedly suggested that genes related to immune inflammatory responses contribute to susceptibility to schizophrenia.[2] Genome-wide association studies (GWAS) have recently become feasible, covering hundreds of thousands of markers.[3-11] A single nucleotide polymorphism (SNP) near the *colony stimulating factor, receptor 2 alpha* (*CSF2RA*) gene is most strongly associated with schizophrenia in GWAS, and an independent case-control study has replicated associations between *CSF2RA* and its neighbor *interleukin 3 receptor alpha* (*IL3RA*) and schizophrenia.[3] Three large-scale GWAS have indicated an association between a major histocompatibility complex (MHC) region at 6p and schizophrenia as well.[4-6] Epidemiological studies have provided strong (but not always consistent) evidence for the environmental influence of obstetric complications such as maternal infection during pregnancy and neonatal hypoxia on schizophrenia risk.[12-14] Based on these findings, animal models of schizophrenia have been established involving obstetric complications.[15] For example, maternally infecting animals with influenza or injecting with double-strand RNA polyinosinic-polycytidylic acid (poly I:C) has been found to induce schizophrenia-like behavioral and neuropathological features in offspring.[16,17] The findings from genetic, epidemiological and animal model studies all suggest that immune inflammatory processes should be implicated in the etiology and pathology of this disease.

Cytokines are modulators of immune/inflammatory reactions and regulators for brain development. Pathological induction of cytokines in response to maternal infections have adverse effects on the neurodevelopment of offspring.[18] Cytokine production and signaling are regulated by a variety of genes,[19-25] some of which may confer susceptibility to schizophrenia.[26] Thus, cytokines have emerged as a putative part of a common pathway of genetic and environmental components for vulnerability to schizophrenia.[27-30] In this review,

we summarize the pivotal roles of specific cytokines, such as epidermal growth factor (EGF), interleukin-1 (IL-1), IL-6, and neuregulin-1 (NRG-1), in the pathophysiology of schizophrenia and its animal modeling.

CYTOKINES AND SCHIZOPHRENIA

EGF and its homologues

EGF has several homologues, including transforming growth factor-α (TGF-α), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin, betacellulin, epigen and epiregulin, which are widely distributed in the brain.[31] These cytokines exhibit a neurotrophic influence on dopaminergic neurons; stimulating neurite outgrowth, increasing dopamine uptake, and enhancing long-term survival.[32,33] EGF protein levels are decreased in the prefrontal cortex (PFC) and striatum of patients with schizophrenia, whereas protein levels of ErbB1, one of EGF receptors, are elevated in the PFC.[34] In contrast, decreases have been reported in protein levels of EGF, its receptors (ErbB1 and ErbB2), and tyrosine hydroxylase (TH) in the PFC and striatum of patients with Parkinson's disease (PD).[35] It is of note that the direction of ErbB1 alteration in schizophrenia is opposite to that in PD, suggesting that abnormal increases or decreases of EGF/ErbB1 signaling in might contribute to dopaminergic dysregulation in schizophrenia and PD, respectively. In addition, there is evidence that serum EGF protein levels are decreased in patients with schizophrenia.[34,36] Although one study failed to find such a decrease, serum EGF levels are correlated with the severity of symptoms of patients with schizophrenia.[37] Taken together, these findings suggest that abnormal ErbB1 signaling might be associated with the pathophysiology of schizophrenia.

IL-1

IL-1 is a proinflammatory cytokine that influences neurodegenerative and neuroprotective processes in the brain and involved in the modulation of synaptic plasticity.[38] This cytokine strongly promotes the processing and release of EGF, HB-EGF, and NRG-1, and exhibits cross-talk with ErbB signaling.[39] Both protein and mRNA levels of the IL-1 receptor antagonist (IL-1RN) are decreased in the PFC of patients with schizophrenia, whereas IL-1β levels are not affected.[40] Accordingly, an imbalance between IL-1 and IL-1RN, with a shift toward IL-1 signaling, may exist in the brains of patients with schizophrenia. This cytokine balance shift might represent patients' vulnerability to immune inflammatory reactions, presumably matching to the present cytokine hypothesis of schizophrenia. Concentrations and *in vitro* production of IL-1α, IL-1β and IL-1RN in blood and cerebrospinal fluid (CSF) have been investigated in patients with schizophrenia, but results are inconsistent.[40-61] A recent meta-analysis assessed the collective evidence across individual studies.[62] Blood levels of IL-1RN were found to be increased in patients with schizophrenia, whereas those of IL-1β were not. However, there has been significant heterogeneity for IL-1β levels among studies. Therefore, blood levels of IL-1β should be examined in as many homogeneous individuals as possible. Intriguingly, serum levels and peripheral blood mononuclear cell (PBMC) mRNA expression of IL-1β are increased in antipsychotic-naïve patients with first-episode schizophrenia.[63]

Following receptor binding, IL-1 activates two signal transduction cascades, inhibitory κB (IκB)/nuclear factor-κB (NF-κB) and p38 mitogen-activated protein (MAP) kinase/jun. Of note, activation and mRNA expression of NF-κB are increased in schizophrenia patients, and NF-κB activation is correlated with *IL-1β* mRNA expression in both patient and control groups.[63] These findings suggest that an abnormal increase in IL-1 signaling might be related to the inflammatory status of patients with schizophrenia.

NRG-1

NRGs constitute a family of factors that perform many functions during neural development, such as promoting the migration and differentiation of γ-amino butyric acid (GABA) neurons, dopaminergic neurons, and oligodendrocytes.[64-67] The abnormal expression of NRG-1 mRNA and protein has been reported in the brain and peripheral blood of patients with schizophrenia.[68-75] In the dorsolateral PFC and hippocampus of patients, mRNA levels of the *NRG1* type I isoforms are increased.[68,69] The results of studies of NRG-1 protein expression are inconsistent, however.[70-72] Interestingly, NRG-1 stimulation in schizophrenia patients has been found to induce pronounced activation of ErbB4, one of the NRG-1 receptors, and to suppress *N*-methyl d-aspartate (NMDA) receptor activation in the PFC.[72] ErbB4 mRNA and protein are also robustly expressed in the midbrain dopaminergic neurons of mice, monkeys and humans, [76,77] and NRG-1 has been shown to promote the development and function of these neurons through activating ErbB4.[78] Taken together, these findings suggest that impaired NRG-1/ErbB4 signaling may also contribute to glutamatergic and dopaminergic dysregulation in schizophrenia.

NRG1 is one of the most promising candidate genes for schizophrenia.[79] In the last several years, numerous studies have confirmed this association,[80-93] but not all reports have been consistent.[94-99] The most recent meta-analysis indicated a weak but significant association between three markers of *NRG1* and schizophrenia: SNP8NRG221132, 420M9-1395(0) and 478B14-848(0).[100] Of note, there is evidence that SNP8NRG1243177 in

the promoter region of the *NRG-1* type IV isoform is associated with mRNA expression of the type IV isoform *in vitro*[101] and in the hippocampus.[69] as well as with serum NRG-1 protein levels (Shibuya et al., unpublished data), psychotic symptoms,[102] spatial working memory capacity,[103] and white matter density and integrity.[104] Thus, SNP8NRG1243177 appears likely to influence the capacity to produce NRG-1 and the endophenotypes for schizophrenia.

IL-6

In the central nervous system, IL-6 has been found to regulate brain development, synaptic plasticity, and various behaviors related to feeding, sleep and stress.[105] Increased blood levels of IL-6 are one of the most frequently confirmed immunological features associated with schizophrenia,[41,47,48,59,106-110] although contradictory findings have also been reported.[42,53,55,57,61,111-115] Studies testing the levels of blood soluble IL-6 receptor (sIL-6R) in patients with schizophrenia have produced inconsistent results.[47,108-110,112,116] A recent meta-analysis indicated that there is an increase in blood levels of IL-6 in schizophrenia, but no alteration in sIL-6R.[62] Interestingly, sIL-6R levels in both serum and CSF are correlated with the severity of paranoid-hallucinatory symptoms of patients.[116] Accordingly, a pathological link between IL-6 signaling and schizophrenia is noteworthy but awaits further investigation.

The potential role of IL-6 in the neurobiological mechanisms underlying schizophrenia has been investigated using animal models. In the poly I:C model for maternal viral infection, schizophrenia-like behavioral abnormalities are prevented by coadministration of anti-IL-6 antibody in pregnant mice, and are not observed in the adult offspring of *Il6* knockout dams.[117] Moreover, a single maternal injection of IL-6 during pregnancy causes schizophrenia-like behavioral abnormalities. IL-6 is responsible for superoxide-induced loss of GABAergic phenotype of parvalbumin-positive interneurons in an established model using the NMDA receptor antagonist ketamine.[118] These findings suggest a potential pathological link between hyper-IL-6 signaling and vulnerability to oxidative stress, which might be associated with GABAergic dysfunction in the brain of patients with schizophrenia.

Cytokine hypothesis of schizophrenia

There are abnormal expression levels of some cytokines in both the brain and peripheral blood of patients with schizophrenia. It is noteworthy that several DNA microarray studies indicate reductions in the expression of genes related to oligodendrocyte and myelination including *ERBB3* in the brains of patients with schizophrenia.[119-125] In addition, dysregulation of genes related to the immune and inflammatory system has also been reported.[124,126,127] Based on these findings, we propose a cytokine hypothesis of schizophrenia, predicting that perturbed cytokine signaling plays a pivotal role in the pathophysiology of this disease. We hypothesize that genetic and environmental factors directly and/or indirectly impair cytokine signaling, leading to abnormal brain development. Then, after adolescence, severe brain dysfunction underlying full-blown schizophrenia is ultimately manifested.

NEONATAL CYTOKINE TREATMENT MODEL OF SCHIZOPHRENIA

Abnormal neurobehavioral development in rodents treated with cytokines as neonates

Because of the limitations of the experimental approach in humans, it is essential to establish appropriate animal models to examine the alternative hypotheses of schizophrenia, to understand the pathophysiology of this disease, and to develop novel biological therapies for schizophrenia. To test the cytokine hypothesis of schizophrenia, the impact of cytokine challenge on neurobehavioral development has been evaluated by a series of animal experiments.[78,128-132] In these studies, sublethal doses of cytokines have been subcutaneously administered during postnatal day 2 to 10 in rats or mice. Neurobehavioral tests are then performed in the pre-pubertal stage (postnatal three weeks) and/or the post-pubertal stage (postnatal eight weeks). These animal experiments have revealed that neonatal cytokine challenges induce distinct abnormalities in neurobehavioral development, depending upon the type of cytokine administered (Table 1).

Neonatal EGF treatment accelerates tooth eruption and eyelid opening. This has been described by Cohen[133] after isolating EGF, which was originally named tooth-lid factor. IL-1 as well as other ILs is known transactivators for ErbB1 via ectodomain shedding of precursors of its ligands.[39] In the pre-pubertal stage, horizontal locomotor activity under novel conditions is increased in rats treated with IL-2, whereas it is decreased in rats treated with interferon-γ (IFN-γ) or leukemia inhibitory factor (LIF). However, these abnormalities disappear in the post-pubertal stage. EGF-treated rats exhibit higher vertical locomotor activity only in the post-pubertal stage. Startle responses to 120 dB acoustic stimuli are elevated in rats treated with ErbB1 ligands (EGF, epiregulin and TGF-α) or IL-1α in the post-pubertal stage.

Prepulse inhibition (PPI) is a phenomenon in which a weak prepulse stimulus attenuates the response to a

Table 1. Neonatal exposure to cytokines and neurobehavioral development in rodents

Cytokine	Locomotor		Startle		PPI		Social interaction
	3 weeks	8 weeks	3 weeks	8 weeks	3 weeks	8 weeks	8 weeks
EGF[#]	=	(H)	=	H	=	L	L
Epiregulin[•]	ND	=	ND	H	ND	L	ND
IFN-γ[#]	L	=	=	=	=	=	=
IL-1α[#]	=	=	=	H	=	L	H
IL-2[#]	H	=	=	=	=	=	=
IL-6[#]	=	=	=	=	=	=	=
LIF[#]	L	=	=	=	=	L	ND
NRG-1[•]	ND	=	ND	=	ND	=	L
TGF-α[•]	ND	=	ND	H	ND	L	ND
TNF-α[#]	=	=	=	=	=	=	=

PPI, prepulse inhibition; EGF, epidermal growth factor; IL, interleukin; IFN, interferon; LIF, leukemia inhibitory factor; NRG, neuregulin; TGF, transforming growth factor; TNF, tumor necrosis factor. = represents no significant alteration. H and L indicate increased and decreased performance, respectively. (H) represents increased rearing activity. ND, not determined. [#]tested in rats. [•]tested in mice.

subsequent startling stimulus.[134,135] Reduced PPI has been found in patients with neuropsychiatric disorders, including schizophrenia.[134,135] Reduction of PPI levels in these patients is thought to reflect impaired function of sensorimotor gating. PPI can be tested in humans and rodents in similar fashions and is widely used in experiments to assess the face validity of animal models of schizophrenia. Neonatal treatment with ErbB1 ligands, IL-1α, NRG-1 or LIF has been found to cause a decrease in PPI in the post-pubertal stage. This PPI abnormality is independent of the increase in acoustic startles, however.[130,131] It is of note that second generation antipsychotics (SGA) such as clozapine and risperidone have been found to reduce PPI deficits in rodents treated with EGF, IL-1α or NRG-1.

Rodents treated with EGF, IL-1α or NRG-1 as neonates display other schizophrenia-like behavioral abnormalities but not learning disability in the post-pubertal stage. Latent inhibition (LI) is the ability to ignore irrelevant stimuli, and is disrupted in patients with schizophrenia.[136] Similarly, LI is impaired in mice treated with NRG-1.[78] In addition, neonatal NRG-1 treatment induces enhanced sensitivity to methamphetamine. Rats treated with EGF also exhibit hypersensitivity to psychostimulants (cocaine and methamphetamine)[137] and the dopamine D2-like agonist quinpirole.[138] Social interaction time is increased in rats treated with IL-1α, whereas that is decreased in rodents treated with EGF or NRG-1. Therefore, significant differences in behavioral traits have been reported in studies based on these different cytokine models.

In addition, the neonatal cytokine treatment model of schizophrenia is currently being developed in non-human primates. A cynomolgus monkey treated with EGF as a neonate was found to exhibit behavioral abnormalities such as hyperactivity and self-injury after adolescence.[139] These behavioral abnormalities are ameliorated by subchronic treatment with risperidone. The findings of these animal studies indicate that among many cytokines examined, neonatal treatment with EGF, IL-1α or NRG-1 produces the long-lasting schizophrenia-like behavioral abnormalities, some of which are ameliorated by SGA.

Analysis of neurobiological mechanisms underlying schizophrenia using the neonatal cytokine treatment model

Cytokines administered subcutaneously to rat and mouse neonates efficiently penetrate the blood-brain barrier (BBB) and trigger their downstream signaling pathways in the brain.[78,128-132,140,141] In comparison, when IL-1α is administered to juveniles (postnatal day 14 to 22), BBB permeation is limited and schizophrenia-like behavioral abnormalities are not manifested in the post-pubertal stage.[130] Therefore, it appears to be necessary for peripherally administered cytokines cross the BBB during neonatal stage in order for schizophrenia-like behavioral abnormalities to emerge in the post-pubertal stage. An important question is whether cytokines administered directly to the brains of adult rats in which the BBB is fully developed, also leads to schizophrenia-like behavioral abnormalities. As might be expected, EGF infusion to the striatum of adult rats has been found to lower PPI and to impair LI.[142] However, these deficits are reversible and are extinguished by the cessation of EGF infusion. In contrast, decreased PPI levels are persistent after puberty in rats treated with cytokines as neonates.[128,129] As such, peripheral cytokine exposure in fetuses would be expected to lead to similar behavioral impairments.

Neonatal rodents have immature brains compared with human neonates. With respect to the neurodevelopmental schedule, the neonatal period (postnatal day 2 to 10) in rats appears to be equivalent to the middle gestational period of human fetuses.[143] If it is possible to extrapolate the findings on the above cytokine models to humans, human fetuses exposed to high concentrations of cytokines would subsequently exhibit neurobehavioral developmental dysfunctions. The levels of cytokines including EGF, IL-1β and IL-6 in the

Table 2. Effects of neonatal EGF/IL-1α treatment on neurobehavioral development in different mouse strains

Strain	Locomotor	Startle	PPI
C3H/He	=/=	H/L	=/=
C57BL/6	=/=	H/=	L/L
DBA/2	H/H	H/H	L/L
ddY	L/=	=/=	=/=

EGF, epidermal growth factor; IL, interleukin; PPI, prepulse inhibition. = represents no significant alteration. H and L indicate increased and decreased performance, respectively.

amniotic fluid are elevated in patients who experience premature rupture of membranes during pregnancy, one of the most serious obstetric complications, even when intrauterine infection cannot be confirmed.[144] It is likely that cytokines in human fetuses transmit peripheral immune/inflammatory signals through the developing BBB to their immature brains, and perturb the structural and functional development of the brain (e.g. GABA neurons and dopaminergic neurons).

One of the most common approaches in modeling the gene-environmental interactions relevant to schizophrenia is to compare the neurobehavioral consequences of neonatal manipulations (e.g. hippocampal lesions and viral infection) among different strains of rodents.[145] Neonatal cytokine treatment induces distinct phenotypes depending on genetic background (Table 2).[140,141] Among four strains (C3H/He, C57BL/6, DBA/2 and ddY) examined, DBA/2 mice are the most sensitive to the cytokines, exhibiting pervasive behavioral alterations such as accelerated horizontal locomotor activity, elevated startle responses, and reduced PPI. It is of note that the strain-dependent behavioral sensitivity to neonatal treatment with EGF or IL-1 is correlated with basal ErbB1 phosphorylation or IL-1-triggered acute signaling in the brain, respectively. These complex gene-cytokine interactions might explain a portion of the pathological heterogeneity of schizophrenia.

To understand the neurobiological mechanisms underlying schizophrenia, the effects of neonatal EGF treatment on developing neurons have been investigated using electrophysiological and biochemical techniques. In the striatum, EGF increases in dopamine metabolism and TH expression have been revealed.[35,128] A similar neurotrophic effect of NRG-1 on midbrain dopaminergic neurons has also been reported.[78] In the ventral tegmental area, EGF enhanced excitatory synaptic input to dopaminergic neurons.[146] The elevation of glutamate receptor expression may result in higher excitability of dopaminergic neurons,[146] which is implicated in hyper-dopaminergic function associated with schizophrenia. In the dentate gyrus, EGF attenuates GABAergic synaptic outputs to granule cells and decreases the protein levels of vesicular GABA transporters.[147] Both *in vivo* and *in vitro*, ErbB1 ligands such as EGF, HB-EGF and TGF-α all reduce the protein expression of GluR1, most prominently in parvalbumin-positive GABAergic neurons.[148-150] These findings indicate a potential pathological link between hyper-ErbB1 signaling and GABAergic dysfunction and hyper-dopaminergic dysregulation. In the neocortex, EGF and its homologue amphiregulin attenuate the expression of synaptic scaffolding proteins such as glutamate receptor interacting protein 1 and synapse-associated protein 97 kDa (SAP97).[151] These findings are consistent with the results of a postmortem brain study showing that the postsynaptic proteins SAP97 and GluR1 are decreased in the PFC of patients with schizophrenia.[152] These reports suggest that aberrant synaptic development triggered by cytokines may be associated with this disease as well.

The findings of animal experiments and postmortem brain studies suggest that perturbed ErbB1 signaling in either prenatal or perinatal stages may induce aberrant development or function of dopaminergic and GABAergic neurons which is strongly implicated in the neuropathology of schizophrenia.[153] Interestingly, ventral forebrain specific *Hb-egf* knockout mice exhibit schizophrenia-like behavioral abnormalities, life-long decreases in the ErbB1 signal cascade, and reductions in protein levels of NR1 and postsynaptic protein-95 in the PFC.[154] Brain function might be impaired in states of both hyper- and hypo-ErbB1 signaling, resulting in counterintuitive behavioral similarities between the neonatal EGF treatment model and *Hb-egf* knockout mice. Further elucidation of the mechanisms of cytokine signaling involved in altering brain structure and function will facilitate understanding of the pathophysiology of schizophrenia.

Search for novel antipsychotic candidates based on the cytokine hypothesis of schizophrenia

According to the cytokine hypothesis of schizophrenia, anti-inflammatory agents may have beneficial efficacy in the treatment of patients. Minocycline, a second-generation tetracycline, has been found to attenuate PPI deficits in an animal model using the NMDA receptor antagonist MK801 (dizocilpine).[155,156] In a six-month, double-blind,

randomized, placebo controlled trial, concomitant treatment with minocycline and SGA produced greater improvement in the negative and cognitive symptoms of patients with early-phase schizophrenia than SGA alone.[157] Celecoxib, a cyclooxgenase-2 inhibitor, ameliorates impairments in PPI and LI induced by the striatal administration of EGF in adult rats.[142] In an eight-week, double-blind, randomized and placebo controlled trial, celecoxib added to risperidone surpassed risperidone in the treatment of positive and general psychopathological symptoms of patients with chronic schizophrenia.[158] The results of these clinical trials suggest that anti-inflammatory agents may serve as promising adjunctive drugs in the treatment of schizophrenia.

Potential candidates for novel antipsychotics have been identified by studies using the neonatal cytokine treatment model of schizophrenia. Subchronic oral administration of emodin, a broad tyrosine kinase inhibitor, has been found to suppress acoustic startle responses and abolish PPI deficits in the neonatal EGF treatment model.[159]. These findings suggest that the effects of emodin on abnormal sensorimotor gating in the neonatal EGF treatment model might be ascribed to its inhibitory action on EGF/ErbB signaling. In addition, a quinazoline derivative, which is an ErbB1 inhibitor and was developed as an anticancer agent, has similar therapeutic effects in this model.[160] Intensive research into the molecules involved in modulating cytokine signals may aid the development novel classes of antipsychotics that can provide optimum outcomes for patients suffering from schizophrenia.

CONCLUSIONS

Taken together, human studies and animal models have provided cumulative evidence for the cytokine hypothesis of schizophrenia (Fig. 1). Bacterial and viral infections during either the prenatal or perinatal stages have been found to induce several cytokines and activate immune cells via the molecular recognition of MHC antigens. The strength of cytokine gene induction varies depending on functional SNPs of their genome. Precursor proteins of cytokines are processed by various types of proteases, and mature peptides are then released. Blood cytokines can partially penetrate the BBB and bind to receptors on neurons and glial cells in the brain. Subsequently, they perturb normal intracellular signaling and influence neurotransmission, neural circuit formation and synapse maturation. We propose that an abnormality in this process results in impaired of brain function and ultimately leads to the development of schizophrenia.

It is our hope that future investigation based on the cytokine hypothesis of schizophrenia will increase knowledge of the underlying biological mechanisms of this complex and poorly understood disease, and ultimately lead to the development of fundamental therapies allowing patients to overcome this devastating disease.

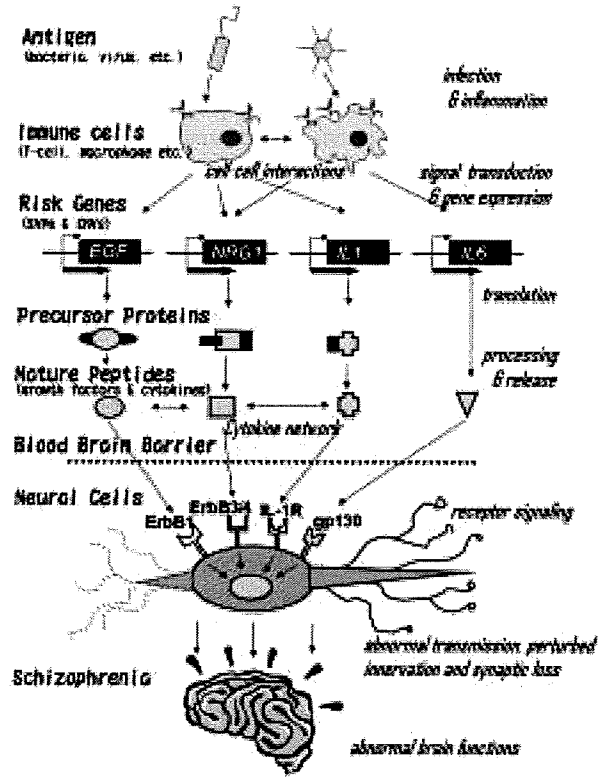

Figure 1. The cytokine hypothesis of schizophrenia. Schizophrenia involves the complex interactions between cytokines and among immune, gene, and neural networks. Antigen; molecules such as bacteria and viruses activating the immune inflammatory system. Immune cells; T cells, B cells, macrophages and natural killer cells, reacting to various cytokines and/or producing them. Risk genes; genes conferring susceptibility to complex disorders including schizophrenia. Precursor proteins; biologically inactive proteins of cytokines processed by various types of proteases in a regulatory fashion. Mature peptides; biologically active forms of cytokines released into circulating blood. Blood-brain barrier: a barrier protecting the brain from immune inflammation in the peripheral blood. Neural cells; neuron and glial cells (astrocyte, microglia and oligodendrocyte), expressing cytokine receptors. Schizophrenia; a severe and chronic mental disorder stemming from impaired development of neurons and their synapses.

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