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/=	=/=	=/=

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

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

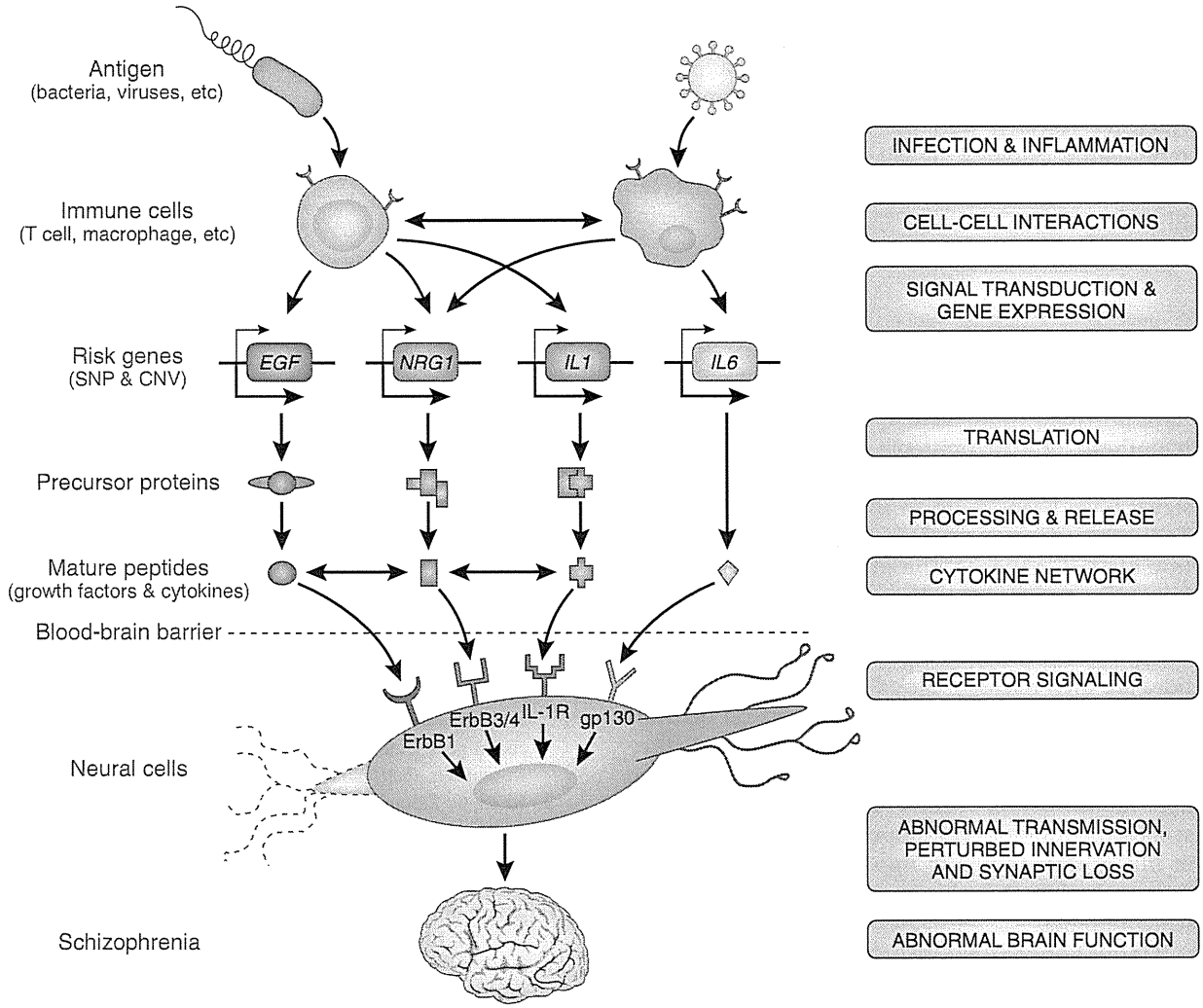

Figure 1. The cytokine hypothesis of schizophrenia. Schizophrenia involves the complex interactions between cytokines and among immune, gene, and neural networks. Antigen, molecules such as bacteria and viruses activating the immune inflammatory system; immune cells, T cells, B cells, macrophages and 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. EGF, epidermal growth factor; IL, interleukin; NRG1, neuregulin-1.

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 of 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 SNP 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 impairment 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 condition.

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