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Altered growth factor signaling pathways as the basis of aberrant stem cell maturation in schizophrenia

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Abbreviations:
ACPT, acid phosphatase, testicular
APC, adenomatous polyposis coli
BCL, B-cell lymphoblastic leukemia
BDNF, brain-derived neurotrophic factor
BMP, bone morphogenic protein
CA, Cornus Ammonis
CDK, cyclin-dependent kinase
CK, casein kinase
CNV, copy number variation
DISC, disrupted in schizophrenia
DKK, dickkopf
Dlx, Distal-less homeobox
ErbB, erythroblastic leukemia viral oncogene homolog
FZD, frizzled
GSK3, glycogen synthase kinase 3
4ICD, ErbB4 intracellular domain
NRG, neuregulin
NTR, neurotrophin receptor
SMAD, similar to mother against decapentaplegic
SNP, single nucleotide polymorphism
TGFBR, transforming growth factor beta receptor
TNF, tumor necrosis factor
Trk, tyrosine receptor kinase
RPTP, receptor tyrosine phosphatase
Wnt, Wingless/Int oncogene

ABSTRACT

In recent years evidence has accumulated that the activity of the signaling cascades of Neuregulin-1, Wnt, TGF-β, BDNF-p75 and DISC1 is different between control subjects and patients with schizophrenia. These pathways are involved in embryonic and adult neurogenesis and neuronal maturation. A review of the clinical data indicates that in schizophrenia the Wnt pathway is most likely *hypoactive*, whereas the Nrg1–ErbB4, the TGF-β- and the BDNF-p75-pathways are *hyperactive*. Haplo-insuffiency of the *DISC1* gene is currently the best established schizophrenia risk factor. Preclinical experiments indicate that suppression of DISC1 signaling leads to accelerated dendrite development in neuronal stem cells, accelerated migration and aberrant integration into the neuronal network. Other preclinical experiments show that increasing NRG1-, BDNF- and TGF-β signaling and decreasing Wnt signaling, also promotes adult neuronal differentiation and migration. Thus deviations in these pathways detected in schizophrenia could contribute to premature neuronal differentiation, accelerated migration and inappropriate insertion into the neuronal network. Initial clinical findings are confirmatory: neuronal stem cells isolated from nasal biopsies from schizophrenia patients display signs of accelerated development, whilst increased erosion of telomeres and bone age provide further support for accelerated cell maturation in schizophrenia.

Contents

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1. Introduction

Schizophrenia is a brain disorder that affects about one in a hundred individuals. The leading hypothesis holds that schizophrenia is the functional consequence of an aberrant neurodevelopment early in life (Murray and Lewis, 1987; Weinberger 1987). After the onset of overt symptoms at puberty, the trajectory of neurodevelopment continues to further deviate (McGrath et al., 2003; Van Haren et al., 2008). Recognition of this progressive course of adult brain development and plasticity is of significance, since restorative therapeutic intervention, in theory, may still be possible after the onset of overt symptoms. In most brain areas cell counts in the schizophrenic brain are not abnormal, but cells are more densely packed owing to a relative dystrophy of their dendritic arborisation and extracellular neuropil (Selemon & Goldman-Rakic, 1999). This suggests that the *de novo* production of neurons, oligodendrocytes and astrocytes is adequate, whereas processes such as insertion into the neuronal network, synaptic pruning, myelination and apoptosis might be aberrant. DISC1 haplo-insuffiency is certainly one of the best established schizophrenia risk factors (Porteous et al., 2006). Suppression of DISC1 signaling leads to accelerated dendrite development in neuronal stem cells, accelerated neuronal migration and inadequate integration into the neuronal network (Duan et al., 2007). These processes are also modified by growth factor signaling cascades and evidence has been accumulating that their functional status is altered in schizophrenia. In the current review I describe in which direction these signaling cascades are modified, and what the functional consequence on neuronal maturation might be. Apart from DISC1, the growth factor pathways which will be reviewed are the 'canonical' Wnt pathway, the NRG1–ErbB4-signaling cascade, BDNF-p75 cascade and the transforming growth factor β pathway.

2. Disrupted in schizophrenia-1 (DISC1)

A Scottish family in which a balanced translocation t(1;11)(q42;q14) co-segregated with major mental disorders with a maximum lod-score of 7.1, was the starting point for the identification of the "disrupted in schizophrenia-1" (*DISC1*) gene at 1q42.1 (St Clair et al., 1990; reviewed in Chubb et al., 2007). This gene encodes a protein of 854 amino acids, with no homology to other proteins of known function. An important observation was that the gene disruption approximately halved the protein levels (Porteous et al., 2006). Linkage and association studies have since been carried out and clearly establish *DISC1* as one of the best validated genetic schizophrenia risk factors (Chubb et al., 2007). Functional studies have shown that DISC1 interacts with proteins of the centrosome, cytoskeleton and transcription factors (Chubb et al., 2007; Matsuzaki & Tohyama, 2007). The consequences of a reduction in DISC1 on adult neurogenesis was investigated in mice by Duan et al (2007). Suppression of the transcription of DISC1 provoked an accelerated migration of neuronal progenitor cells, which led to an inappropriate positioning of new neurons. Importantly, these phenotypical changes could be reverted by reintroduction of DISC1 via exogenous expression. Furthermore, DISC1 suppression accelerated dendritic development of adult neurons and induced earlier functional maturation in terms of GABAergic and glutamatergic synaptic inputs and firing patterns. The functional consequence of this was an aberrant integration of adult-born hippocampal neurons in animals with DISC1 protein level reductions. Knock-down of NDEL1, a protein which interacts with full-length DISC1, but not with the truncated form of DISC1, was found to mimic several of the effects seen with knock-down of DISC1, including the ectopic dendrites and aberrant cell positioning.

3. The NRG1 (type IV)–ErbB4 signaling cascade

The notion that mutation of the *neuregulin-1* gene (*NRG1*) raises the risk for schizophrenia, stems from a genetic association study by Stefansson and colleagues. These authors described a seven-marker risk haplotype in *NRG1* that occurred in 14.4% of Icelandic schizophrenia patients, but also in 7.6% of the Icelandic control population (Stefansson et al., 2003). *NRG1* as a risk factor for schizophrenia has since than been confirmed in several additional populations, although often with different mutations (reviewed by Tosato et al., 2005; Li et al., 2006). Law et al. (2006) discovered that the mutation denoted as rs6994992, a SNP within the Icelandic risk haplotype, was part of the promoter region of a novel NRG1 splice variant (called NRG1 type IV). It resulted in increased mRNA levels of this isoform. Interestingly, unlike other splice variants, NRG1 type IV is exclusively expressed in the brain and particularly abundant in fetal brain (Tan et al., 2007).

Subsequent to the discovery of the gain of function mutation in NRG1 type IV as a risk factor for schizophrenia, the down stream components of this growth factor pathway were investigated. NRG1 signals to three members of the ErbB receptor tyrosine kinase family, ErbB2, ErbB3 and ErbB4. Mutation screening of ErbB4 provided modest evidence for association with schizophrenia (Silberberg et al., 2006) and moreover, there was evidence for a statistical locus by locus interaction between *ErbB4* and *NRG1* genotypes (Norton et al., 2006). The ErbB4 receptor is a 180 kDa transmembrane glycoprotein that becomes autophosphorylated upon NRG1 binding. Four isoforms of ErbB4 are known (Junttila et al., 2000). The isoform named JM-a, is sensitive to proteolytic cleavage by γ-secretase whereby an 80 kDa-large ErbB4 intracellular domain (4ICD) protein is formed (Ni et al., 2003). This 4ICD protein is involved in nuclear signaling and influences cell fate decisions of neuronal stem cells (Sardi et al., 2006). Investigation of the expression of the ErbB4 splice variants revealed that the JM-a form mRNA was significantly overexpressed in dorsolateral prefrontal cortex of schizophrenia patients (Law et al., 2007). ErbB4 protein levels (combined isoforms) were also increased (Chong et al., 2008). A remarkable study by Hahn et al. (2006) investigated NRG1–ErbB4 signaling in human postmortem prefrontal cortex. NRG1-induced tyrosine phosphorylation of ErbB4 was significantly higher in