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BRAIN RESEARCH REVIEWS

Review

Molecular and cellular mechanisms of altered *GAD1/GAD67* expression in schizophrenia and related disorders

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Abbreviations:
BDNF, brain-derived neurotrophic factor
D_2, dopamine receptor D_2-like
GABA, gamma-amino-butyric acid
GAD, glutamic acid decarboxylase
GAD67, 67 kDa isoform of GAD
GAD65, 65 kDa isoform of GAD
GAD1, glutamic acid decarboxylase 1
NCAM, neural cell adhesion molecule
NMDA, N-methyl-D-aspartate
PFC, prefrontal cortex
SNP, single nucleotide polymorphism
TCA, tricarboxylic acid
TrkB, receptor tyrosine kinase B

ABSTRACT

The 67 and 65 kDa isoforms of glutamic acid decarboxylase, the key enzymes for GABA biosynthesis, are expressed at altered levels in postmortem brain of subjects diagnosed with schizophrenia and related disorders, including autism and bipolar illness. The predominant finding is a decrease in GAD67 mRNA levels, affecting multiple brain regions, including prefrontal and temporal cortex. Postmortem studies, in conjunction with animal models, identified several mechanisms that contribute to the dysregulation of GAD67 in cerebral cortex. These include disordered connectivity formation during development, abnormal expression of Reelin and neural cell adhesion molecule (NCAM) glycoproteins, defects in neurotrophin signaling and alterations in dopaminergic and glutamatergic neurotransmission. These mechanisms are likely to operate in conjunction with genetic risk factors for psychosis, including sequence polymorphisms residing in the promoter of *GAD1* (2q31), the gene encoding GAD67. We propose an integrative model, with multiple molecular and cellular mechanisms contributing to transcriptional dysregulation of GAD67 and cortical dysfunction in psychosis.

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Contents

1. Introduction

Dysfunction of cerebral cortex and hippocampus in schizophrenia and related disorders is thought to include alterations in GABAergic, inhibitory neurotransmission (Guidotti et al., 2005; Lewis et al., 2005). The underlying cellular mechanisms include subtle changes in interneuron connectivity (Benes and Berretta, 2001) and a distinct set of molecular and genetic alterations (Harrison and Weinberger, 2005). Among the genes involved in the pathophysiology of cortical dysfunction in schizophrenia is *GAD1* (Rapoport et al., 2005), which encodes the 67 kDa isoform of glutamic acid decarboxylase, the key enzyme for GABA synthesis (Bu et al., 1992). Genetic studies linked *GAD1* to abnormal neurodevelopment and early (childhood)-onset schizophrenia (Addington et al., 2005) and bipolar disorder (Lundorf et al., 2005). Furthermore, subjects diagnosed with psychosis frequently show dysregulated GAD67 and GAD65 expression in cerebral cortex and other brain regions (Akbarian et al., 1995; Blatt, 2005; Dracheva et al., 2004; Fatemi et al., 2002, 2005; Guidotti et al., 2000; Heckers et al., 2002; Torrey et al., 2005; Volk et al., 2000; Woo et al., 2004). As discussed further below, the majority of the studies conducted on postmortem brain tissue from clinical cases report alterations in GAD67 mRNA levels. Therefore, insight into the molecular pathways governing GAD67 gene expression could advance current knowledge on the pathogenesis of psychosis. Studies in animals, complemented by postmortem and other clinical studies, identified several molecular and cellular mechanisms that regulate cortical GAD67 expression. These include changes in neuronal activity, disordered connectivity formation during development, alterations in glutamatergic and dopaminergic neurotransmission and defects in neurotrophin or glycoprotein signaling. This review will summarize, for each of these mechanisms, the relevant findings obtained from animal models and clinical studies. We propose an integrative model to explain GAD67 gene expression changes in psychosis. The model includes allelic polymorphisms in the *GAD1* promoter sequence as genetic susceptibility factors, which operate in conjunction with a defined set of maladaptive molecular mechanisms contributing to cortical dysfunction in psychosis.

2. GAD genes and function

Glutamic acid decarboxylase (GAD) in brain catalyzes synthesis of the inhibitory neurotransmitter gamma-amino butyric acid (GABA). The GABAergic neurons of the mammalian nervous system express two homologous forms of GAD, with protein sizes of 67 and 65 kDa, each encoded by a different gene (Bu et al., 1992; Erlander and Tobin, 1991). It is estimated that GAD67 accounts for 56–85% of the GABA synthesis flux in rat cerebral cortex at baseline (Mason et al., 2001), and up to 80–90% of overall GABA levels in mouse brain (Asada et al., 1997; Condie et al., 1997). The cellular GABA store is compartmentalized into a vesicular pool for synaptic transmission and a cytoplasmic pool. Cytoplasmic GAD is thought to shunt 2-oxoglutarate away from the tricarboxylic acid (TCA) cycle, and provide GABA for the vesicular pool (Hassel et al., 1998) and TCA cycle-mediated oxidation (An et al., 2003; Baxter, 1976). The two GAD isoforms are expressed by GABAergic neurons. Studies on GAD65 null mutant mice suggest that GAD67 is important for the cytoplasmic pool and to a large extend also for the vesicular pool of GABA (Tian et al., 1999). This contrasts with GAD65, which appears to regulate primarily the vesicular pool (Kaufman et al., 1991; Soghomonian and Martin, 1998), especially under conditions of sustained synaptic activity (Tian et al., 1999). In addition, the localization of the two GAD isoforms within neuronal processes is differentially regulated among the different subpopulations of GABAergic neurons (Fukuda et al., 1998; Mackie et al., 2003). Finally, studies in genetically engineered mice revealed that the two GAD isoforms play different roles during development: loss of GAD67 is not compatible with postnatal life due to severe defects in craniofacial development, given that *Gad67(Gad1)* null mutant mice succumb shortly after birth due to complications from cleft palate (Asada et al., 1997; Tsunekawa et al., 2005) in conjunction with malfunction of the