Molecular Genetics and Metabolism 113 (2014) 307–314

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Folinic acid treatment for schizophrenia associated with folate receptor autoantibodies

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ARTICLE INFO

Article history:
Received 29 July 2014
Received in revised form 30 September 2014
Accepted 1 October 2014
Available online 12 October 2014

Keywords:
Autoimmunity
Folate receptor
Treatment
Schizophrenia
Cerebral folate deficiency

ABSTRACT

Background: Auto-antibodies against folate receptor alpha (FRα) at the choroid plexus that block N^5-methyltetrahydrofolate (MTHF) transfer to the brain were identified in catatonic schizophrenia. Acoustic hallucinations disappeared following folinic acid treatment. Folate transport to the CNS prevents homocysteine accumulation and delivers one-carbon units for methyl-transfer reactions and synthesis of purines. The guanosine derivative tetrahydrobiopterin acts as common co-factor for the enzymes producing dopamine, serotonin and nitric oxide.

Methods: Our study selected patients with schizophrenia unresponsive to conventional treatment. Serum from these patients with normal plasma homocysteine, folate and vitamin B12 was tested for FR autoantibodies of the blocking type on serial samples each week. Spinal fluid was analyzed for MTHF and the metabolites of pterins, dopamine and serotonin. The clinical response to folinic acid treatment was evaluated.

Results: Fifteen of 18 patients (83.3%) had positive serum FR auto-antibodies compared to only 1 in 30 controls (3.3%) ($\chi^2 = 21.6$; $p < 0.0001$). FRα antibody titers in patients fluctuated over time varying between negative and high titers, modulating folate flux to the CNS, which explained low CSF folate values in 6 and normal values in 7 patients. The mean ± SD for CSF MTHF was diminished compared to previously established controls (t-test: 3.90; $p = 0.0002$).

A positive linear correlation existed between CSF MTHF and biopterin levels. CSF dopamine and serotonin metabolites were low or in the lower normal range. Administration of folinic acid (0.3–1 mg/kg/day) to 7 participating patients during at least six months resulted in clinical improvement.

Conclusion: Assessment of FR auto-antibodies in serum is recommended for schizophrenic patients. Clinical negative or positive symptoms are speculated to be influenced by the level and evolution of FRα antibody titers which determine folate flux to the brain with up- or down-regulation of brain folate intermediates linked to metabolic processes affecting homocysteine levels, synthesis of tetrahydrobiopterin and neurotransmitters. Folinic acid intervention appears to stabilize the disease process.

1. Introduction

Schizophrenia is a severe mental illness affecting 1% of the population. Clinical recognition is characterized by the presence of phases with positive symptoms (delusions, hallucinations, disorganization of thoughts and speech, catatonic behavior), phases with negative symptoms (affective flattening, alogia, avolition) and cognitive impairment [1,2]. Some neuro-imaging studies documented progressive gray matter loss over 5–10 years [3]. Schizophrenia is a multifactorial disorder carrying a predominant genetic risk as reflected by a positive family history, in addition to environmental risk factors like obstetric complications, social isolation, migrant status and urban life and early exposure to drug abuse like cocaine, amphetamines and cannabis. Schizophrenia fits the model of a complex disorder in which multiple genes interact along with environmental influences, to produce the schizophrenic phenotype. In addition to susceptibility genes involving growth factors participating in nerve growth and development, the encoded proteins by most of the strongest candidate genes are involved in dopamine and glutamate signaling [4–6]. Beyond the older dopamine hypothesis, the NMDA glutamate receptor hypofunction hypothesis has recently gained more interest [7–9].

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http://dx.doi.org/10.1016/j.ymgme.2014.10.002
1096-7192/

Circumstantial evidence supports the earliest hypothesis that positive symptoms in schizophrenia result from overactive mesolimbic dopamine neurons located in the brainstem (ventral tegmental area) leading to overstimulation of their striatal and limbic projection areas. This was suggested by observations that psychotic episodes can be induced by drugs that increase dopamine, such as amphetamine or cocaine, whereas antipsychotic drugs decrease the effect of dopamine overstimulation by blocking D2 receptors. The negative, cognitive and affective symptoms of schizophrenia result from underactive mesocortical dopamine neurons localized in the brainstem which project to the dorsolateral- and ventromedial prefrontal cortex.

The recent hypothesis of NMDA glutamate receptor hypofunction expanded the earlier dopamine hypothesis by providing an explanation for the differences of overactive mesolimbic neurons versus underactive mesocortical dopamine neurons (Fig. 1). In normal individuals, descending cortical glutamatergic pathways project to and activate NMDA-type glutamate receptors on inhibitory γ-aminobutyric acid interneurons in the brainstem thereby mediating tonic inhibition of mesolimbic dopamine neurons in the ventrotegmental area. In schizophrenic subjects, NMDA receptors on inhibitory interneurons become hypoactive resulting in disinhibition of ventrotegmental dopamine neurons, rendering the mesolimbic dopamine pathways hyperactive which creates the positive symptoms of psychosis. In contrast to mesolimbic dopamine neurons, cortico-brainstem glutamate neurons in normal individuals synapse directly upon the mesocortical dopamine neurons and therefore result in tonic excitation of the mesocortical dopamine neurons and their projection to the prefrontal cortex. In schizophrenic subjects, the cortico-brainstem glutamate projections target hypoactive NMDA receptors upon mesocortical neurons which results in loss of tonic excitation of these mesocortical dopamine neurons and their cortical targets. Underactivity of these mesocortical pathways has been linked to the negative, cognitive and affective symptoms [7–11]. Evidence in support of the NMDA-receptor hypofunction hypothesis is the fact that several of the known susceptibility genes for schizophrenia reduce NMDA receptor density or decrease glutamate signaling [4]. Moreover, auto-antibodies against NMDA-receptors have been identified in patients presenting with psychotic symptoms as first manifestations [12–14].

Earlier reports described deranged folate metabolism and disturbed one-carbon transfer associated with schizophrenia [15,16]. Evidence in support of deranged folate metabolism linked to schizophrenia comes from a study in which one-third of patients with major depression or schizophrenia had unexplained borderline or definite red blood cell folate deficiency that improved after high-dose DL-methyltetrahydrofolate treatment [17].

A report of a girl with mild mental retardation and schizophrenic behavior has identified congenital methylene-tetrahydrofolate reductase (MTHFR) deficiency [18].

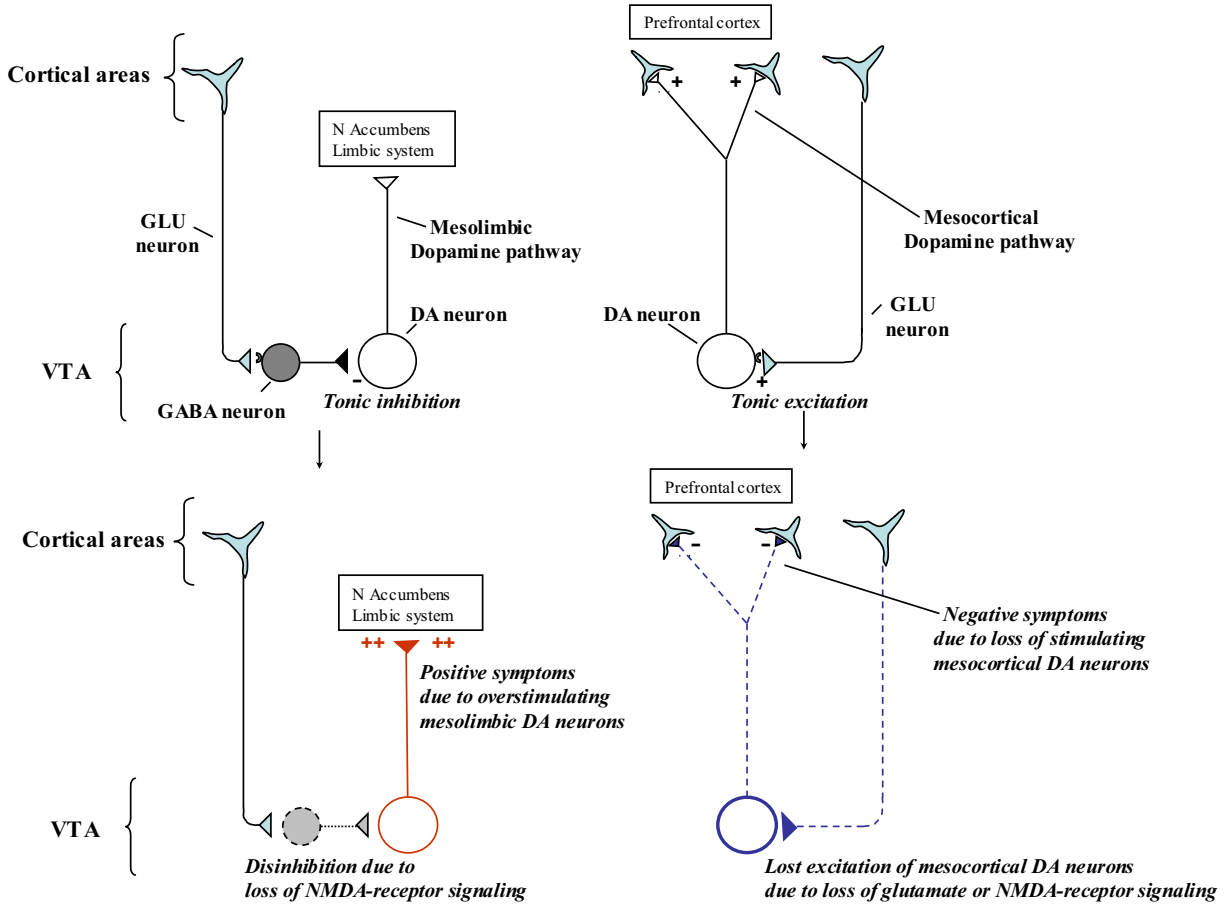

Fig. 1. NMDA-receptor hypofunction hypothesis in schizophrenia. The upper left part of figure depicts normal signaling pathways with tonic inhibition of mesolimbic dopamine neurons in the brainstem ventral tegmental area (VTA) by NMDA-receptor containing inhibiting GABA-ergic interneurons. The loss of NMDA receptor function in these inhibitory GABA interneurons leads to activation of mesolimbic dopaminergic pathway neurons leading to positive symptoms (lower left part). The right upper part is the normal situation where descending cortico-brainstem glutamate neurons exert excitation of the mesocortical dopaminergic neurons. In schizophrenia loss of glutamate or NMDA-receptor mediated signaling leads to understimulation by mesocortical neurons projecting to the prefrontal cortex with resulting negative symptoms (right lower part). Abbreviations: GLU: glutamate; DA: dopamine; VTA: ventral tegmental brainstem area.