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Selected issues of GABA metabolism and its potential role in neuropsychiatric disorders

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ABSTRACT

This mini review is limited to chosen problems about GABA metabolism mainly in aspect of associated disorders. GABA primarily identified as inhibitory neurotransmitter plays also excitatory function. Abundant investigations concern the role of GABA in forming and development of neuronal structures in the brain. Resolving of this basic questions will allow to understand the etiology of related neuropsychiatric disorders.

Keywords: *ABAT*, GABA, interneurons, autism, bipolar disorder, schizophrenia.

Introduction

Gamma (γ)-amino-butyric acid (GABA) is the primary inhibitory neurotransmitter in adult human brain. During early development stages GABA plays both inhibitory and excitatory roles. GABA is created by decarboxylation of glutamic acid, a main excitatory neurotransmitter. There is evidence that GABA level is elevated in bipolar disorder (BP) [1] and impairment of genes involved in GABA metabolism has been linked to neuropsychiatric disorders such as epilepsy, autism and schizophrenia (SZ).

GABA interneurons

GABA producing (GABAergic) interneurons are the only source of GABA and the main source of inhibition in the mammalian central nervous system. GABAergic interneurons control the activity of pyramidal neurons and are responsible for the balance between excitation and inhibition signals in the brain. Depending on the brain region, they constitute 10–25% of the total number of cortical neurons. At least 20 different cortical subtypes and 21 hippocampal subtypes of GABAergic interneurons have been identified [2–4]. GABAergic neurons of the hippocampus are arising before the glutamatergic neurons [5]. They may play a role in the development of the hippocampus in a manner analogous to Cajal-Retzius cells [6]. There is evidence that differentiation of the GABAergic phenotype depends on activity of Dlx genes (*Dlx1/2*). Loss of *Dlx* function eliminates hippocampal GABAergic neurons [7].

Genes involved in GABA metabolism (synthesis, transport and decay)

GABA synthesis is controlled by two glutamic acid decarboxylases (GADs) – GAD67/65 encoded by *GAD1/2*, respectively. The two genes produce a number of alternative transcripts. As GADs are not expressed in the astrocytes these cells cannot synthesize GABA from glutamic acid. This process is possible after transforming glutamate into glutamine (in reaction catalysed by glutamine synthetase) which is then transferred by specific transporter to presynaptic terminal containing GADs [8]. Diminished level of GADs was observed in cortex of autistic persons [9]. GABA loaded into synaptic vesicles by the vesicular GABA transporter (encoded by *SLC32A1*) is secreted by exocytosis into the synaptic cleft. GABA inactivation is performed by reuptake into presynaptic membrane or into astrocyte controlled by GABA transporters: GAT-

1,GAT-2, GAT-3 and BGT-1, depended on Na^+/Cl^- ions. In human cortex GAT-1 and GAT-3 transporters are expressed. Decomposition of GABA depends on activity of GABA transaminase.

The GABA receptors

GABAergic neurotransmission is mediated by GABA receptors. There are fast receptors: $GABA_A$ and $GABA_C$ which are ionotropic Cl^- channels and slow ones – metabotropic $GABA_B$ G protein-coupled receptor. $GABA_A$ is the only GABA receptor whose subunit (α3) pre-mRNA is edited by adenosine deaminase [10]. This modification diminishes Cl^- current through the receptor [11]. $GABA_B$ plays a role of autoreceptor which inhibits neurotransmitter release through inhibition of calcium channels. Postsynaptically located $GABA_B$ produces slow inhibitory potentials through G protein–coupled inward rectifying potassium channels. GABA receptors are involved in the pathogenesis of absence and temporal lobe epilepsies, autism and SZ [12, 13].

The GABA transaminase

GABA transaminase (GABA-T) acts as a dimer protein in the mitochondrial matrix (monomer contains 500 amino acids). GABA-T catalyses amino group transfer from GABA to alpha-ketoglutarate using pyridoxal phosphate as a cofactor. This process generates glutamate and succinic semialdehyde which after converting to succinic acid is utilized by Krebs cycle. GABA-T locates to the 4-aminobutyrate aminotransferase gene -*ABAT* at chromosome 16p13.2. Genetic disorder associated with *ABAT* is GABA-T deficiency. This is unique recessive disorder (only three cases described) whose symptoms (severe early infantile epileptic encephalopathy and growth acceleration) are evoked by cerebral accumulation of GABA [14]. The diagnosis based on measuring of cerebral GABA concentrations may be performed non-invasively by magnetic resonance spectroscopy [15]. Recent findings reveal that GABA-T is also involved in the conversion of dNDP to dNTP within mitochondria and every case of GABA-T deficiency is associated with mitochondrial DNA depletion syndrome [16].

The role of GABA – inhibition and excitation

Primary role of GABA is the inhibitory neurotransmition in adult human brain. GABA acts postsynaptically by increasing membrane conductance to chloride ions. It results in inhibition of the generation of an action potential in postsynaptic cell. During early development stages GABA plays both inhibitory and excitatory roles. Excitatory actions of GABA are important for proliferation, migration, synaptogenesis, neuronal differentiation and neuronal network stability [2]. One of the conditions for excitatory GABAergic transmission is the negativity of the resting membrane potential (V_m) relative to the chloride equilibrium potential (E_{Cl}). This excitatory action of GABA in embrional neurons is enabled by the expression of sodium-potassium chloride cotransporter (NKCC1). NKCC1 uses the inward Na^+ gradient maintained by the Na^+ pump to transport Cl^- into the cell. The increase of intracellular Cl^- results in E_{Cl} that is more positive than V_m. Activation of $GABA_A$ receptor produces Cl^- efflux, resulting in membrane depolarization (excitation). During neuronal maturation GABA converts its action from excitatory to inhibitory due to the expression of the K^+/Cl^- cotransporter KCC2. This protein produces active chloride efflux reducing intracellular Cl^- concentrations. As a result E_{Cl} is more negative than V_m and activation of $GABA_A$ receptor produces Cl^- influx leading to membrane hyperpolarization (inhibition) [2]. GABA mediates excitatory actions in immature neurons, adult dorsal root ganglion, and the adult pyramidal cells of cornu ammonis 1 hippocampal subfield – a region critically involved in the pathophysiology of SZ [17, 18].

Epigenetic regulation of GABAergic genes

Recent study in SZ and BP point to a downregulation in the expression of several genes in GABAergic interneurons very probably caused by gene promoter hypermethylation mediated by overexpression of DNA methyltransferases (DNMTs) in these cells. DNMTs catalyze the transfer of a methyl group from the methyl donor S-adenosylmethionine (SAM) to the carbon 5' of cytosines embedded in cytosine phosphodiester guanine (CpG) islands of many gene promoters. SZ and BP disorder could be associated with the epigenetic downregulation of genes expressed in GABAergic neurons: GAD67and reelin – an extracellular large (400 kDa) matrix protein that regulates neuronal migration and positioning in the developing brain. Aberrant epigenetic mechanisms in the pathogenesis of SZ and BP are supported by observations that downregulated expression of GAD67 or reelin in GABAergic neurons

of the patients is associated with an overexpression of zNMTs (DNMT1 and DNMT3a). Valproic acid – an antipsychotic drug that enhances GABAergic transmission can reverse promoter hypermethylation [19].

Other genetic disturbances of GABA metabolism as the cause of neuropsychiatric disorders

Alternate transcripts from neuron-specific K^+/Cl^- cotransporter KCC2 gene (*SLC12A5*) may participate in the abnormal GABA signaling in SZ [20]. Succinic semialdehyde dehydrogenase (SSADH) is an enzyme catalyzing oxidation of succinic semialdehyde (generated in reaction catalysed by GABA-T) to succinic acid. SSADH locates to the aldehyde dehydrogenase 5 family, member A1 gene (*ALDH5A1*) at chromosome 6p22.3. The *ALDH5A1* associated disorder – SSADH deficiency identified in hundreds of persons worldwide is much more common than GABA-T deficiency. In the absence of SSADH succinic semialdehyde is reduced by 4-hydroxybutyrate dehydrogenase to gamma hydroxybutyric acid which is a potential neurotoxic agent. SSADH deficiency symptoms are: early hypotonia and developmental delays, later expressive language impairment and obsessive-compulsive disorder, nonprogressive ataxia, hyporeflexia, and epilepsy [14]. The mutations of MECP2 protein (that binds to methylated DNA during transcriptional silencing) are cause of Rett syndrome – an X-linked disorder associated with motor impairment and autism-like symptoms. MeCP2 deficiency in GABAergic neurons is associated with reduced GAD67/65 (*GAD1/2*) levels leading to reduction in presynaptic GABA release. This suggests that impairment of GABA synthesis may be responsible for neuropsychiatric symptoms in Rett syndrome [21].

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Conflict of interest statement
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