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Review

GABA system dysfunction in autism and related disorders: From synapse to symptoms

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ABSTRACT

Autism spectrum disorders (ASDs) are neurodevelopmental syndromes characterised by repetitive behaviours and restricted interests, impairments in social behaviour and relations, and in language and communication. These symptoms are also observed in a number of developmental disorders of known origin, including Fragile X Syndrome, Rett Syndrome, and Foetal Anticonvulsant Syndrome. While these conditions have diverse etiologies, and poorly understood pathologies, emerging evidence suggests that they may all be linked to dysfunction in particular aspects of GABAergic inhibitory signalling in the brain. We review evidence from genetics, molecular neurobiology and systems neuroscience relating to the role of GABA in these conditions. We conclude by discussing how these deficits may relate to the specific symptoms observed.

Contents

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1. Introduction

Autism spectrum disorders (ASDs) are a group of common neurodevelopmental syndromes. ASDs are diagnosed on the basis of qualitative behavioural abnormalities in three domains: social interaction, language and communication, and repetitive or restricted interests or behaviours (American Psychiatric Association, 2000).

ASD symptoms are also observed in a number of neurodevelopmental disorders of known aetiology, including Fragile X Syndrome, Rett Syndrome, and Foetal Anticonvulsant Syndrome. While these disorders have very different underlying etiologies, their overlapping symptom profiles suggest that they may share a final common neurobiological pathway, which may also be present in idiopathic ASDs. However, the nature of this pathophysiology remains unclear.

Emerging evidence suggests that this pathway critically involves impairments in particular aspects of inhibitory gamma-aminobutyric acid (GABA) neurotransmission. In this paper, we review the evidence of abnormalities in GABAergic neurons and synapses in neurodevelopmental disorders characterised by a shared symptomatology of ASD symptoms. A number of previous reviews have discussed selected aspects of this topic in detail, such as the evidence from molecular neurobiology and animal models (D'Hulst and Kooy, 2007; Pizzarelli and Cherubini, 2011; Rossignol, 2011; Sgado et al., 2011). However, few authors have attempted to integrate this literature with the evidence from studies of human patients. The question of the mechanisms by which the hypothesised GABA deficits give rise to the characteristic symptoms of these disorders in humans, has likewise rarely been raised.

In this paper, we begin by presenting a concise overview of the neurobiology of the human GABA system. See Fig. 1 for a graphical overview of the main components of this system. We then examine the evidence relating to the hypothesis that ASD and related disorders are characterised by particular abnormalities in this system. We conclude by discussing how these abnormalities might relate to the particular clinical features seen in these syndromes.

2. The GABA system

2.1. GABA metabolism, release and reuptake

GABA (gamma-aminobutyric acid) is the primary inhibitory neurotransmitter in the adult human brain. An amino acid transmitter, GABA is synthesised from the excitatory neurotransmitter glutamate via the action of glutamate decarboxylase (GAD) enzymes, of which there are two main isoforms, GAD_{65} and GAD_{67}.

Release of synaptic GABA depends upon the loading of GABA into synaptic vesicles, which is performed by the vesicular inhibitory amino acid transporter (VIAAT) (Gasnier, 2004). Following release, reuptake of extracellular GABA into the presynaptic interneurons is performed by the GABA transporter GAT1, and to a lesser extent by the related GAT2 and GAT3 transporters (Madsen et al., 2009). Glial cells, such as astrocytes, are also involved in GABA reuptake that escapes the synapse and this is primarily via GAT3 (Madsen et al., 2009). Following reuptake the breakdown of GABA into glutamate is performed by GABA transaminase (GABA-T) (Madsen et al., 2008).

In the central nervous system, GABA is produced and released by inhibitory interneurons. These are cells of typically small dimensions and small projection fields, although small populations of longer range GABA projections have been reported in the cortex (Tamamaki and Tomioka, 2010). GABAergic interneurons are diverse, and can be differentiated on the basis of either their cytoarchitecture (basket, chandelier, stellate, and others) or their molecular properties (parvalbumin-expressing (PV+), calretinin+, calbindin+, and others). These subtypes have distinct electrophysiological and functional properties (De Marco Garcia et al., 2011; Fu et al., 2011). In addition, the cerebellum contains a distinct set of GABAergic cells, including the very large Purkinje cells (Bailey et al., 1998) and others.

In addition to those proteins involved in GABA synthesis, release and breakdown, as discussed above, many other molecules play a role in the formation and stabilisation of GABAergic synapses, and numerous transcription factors exert indirect effects on GABA function through the regulation of gene expression, receptor trafficking, and downstream signalling pathways (Luscher et al., 2011). The GABA system is therefore vulnerable to genetic perturbation, even if the mutation in question does not directly relate to GABA.

2.2. GABA receptors

GABA acts on two main classes of membrane-bound receptors – ionotropic $GABA_A$ receptors, which are ligand-gated chloride channels, and metabotropic $GABA_B$ receptors.

The $GABA_A$ receptor is composed of five subunits arranged around a central pore (Nutt and Malizia, 2001), derived from a family of different genes which generates a large degree of receptor diversity, with different combinations of subunits giving rise to receptors with specific properties. GABA binding to the $GABA_A$ receptor enhances conductance through the receptor ionophore, which conducts anions, particularly chloride and bicarbonate. The resultant increase of these negatively charged ions within the cell hyperpolarizes the membrane resting potential, thus leading to the inhibition of cell firing under most physiological conditions.

The generation of transgenic mice with point mutations of the benzodiazepine binding site on specific subunits has highlighted the significance of the individual α subunit subtypes in the actions of the benzodiazepines (Rudolph and Mohler, 2004). The α1 subunit receptors appear to be responsible for sedative effects of positive allosteric modulators of the $GABA_A$ system, such as diazepam, α2 and α3 receptors for anxiolytic effects (Low et al., 2000; McKernan et al., 2000; Mohler, 2006; Rudolph et al., 1999) and α5 receptors for cognitive and memory deficits (Collinson et al., 2006; Crestani et al., 2002). The α1, α2, and α3 subtypes are located in synaptic processes, whereas the α5 subtype is located extrasynaptically, where they regulate tonic inhibition along with another receptor type that contains the α4 and δ subunits.