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The role of GABAergic signalling in altered sensory processing in ASD

Abstract

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the adult mammalian brain. The GABAergic system is important for the formation of functional neural networks during development, and is essential in the maintenance of the excitation/inhibition balance, which is crucial for adequate sensory processing. There have been many reports of altered GABA parameters in autism spectrum disorder (ASD), leading to the hypothesis of an excitation/inhibition imbalance as causation of this neurodevelopmental disorder. This altered GABAergic transmission in ASD has been found to be associated to sensory processing abnormalities in the visual, tactile and auditory domains. There are indications that altered sensory processing and abnormalities of the GABAergic system may be involved in the development of the other core domains of ASD: repetitive behaviour and socio-communicative deficits. Nevertheless, the literature shows mixed results regarding the GABAergic system, with some studies showing a decreased GABAergic function while others have found an increased GABA-mediated inhibition. The fact that ASD is a heterogeneous condition, which comprises a wide spectrum of symptomatology, may be a reason for the disparity of the results. However, the combined findings show an abnormal GABAergic inhibition in sensory processing present in ASD, supporting the excitation/inhibition imbalance hypothesis of ASD.

Contents

Introduction

Normal functioning of the GABAergic system

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the adult mammalian brain. This neurotransmitter is synthetized from the excitatory neurotransmitter glutamate by glutamic acid decarboxylase (GAD) enzymes[1], which are present in two different isoforms: GAD_{65} (in synaptic terminals) and GAD_{67} (in the neuronal soma)[2]. GAD_{67} is more abundant than GAD_{65} in most of the brain[3], and is tightly controlled by intraneuronal GABA concentrations, revealing its importance in the regulation of GABAergic function[4]. The GABAergic system consists of interneurons that release GABA and hyperpolarize neurons, inhibiting neurotransmission in neural networks[5]. GABA is released in synapses through the vesicular inhibitory amino acid transporter (VIAAT). After its release, reuptake is mainly regulated by the GABA transporter GAT1, and to some extend by the GAT2 and GAT3 transporters[Error! Bookmark not defined.]. Once the reuptake of GABA has taken place, GABA-transaminase (GABA-T) breaks it down into glutamate.

GABA exerts its action through the binding and activation of membrane-bound $GABA_A$ and $GABA_B$ receptors, which are widely distributed in the brain[2]. $GABA_A$ receptors are integral ion channels, while $GABA_B$ receptors are metabotropic receptors coupled to ion channels through guanine nucleotide-binding proteins and second messengers. Binding of GABA to the ionotropic $GABA_A$ receptor in the mature brain causes them to open and allows the net influx of chloride ions, resulting in an increased membrane hyperpolarisation of the postsynaptic neuron and the inhibition of neuronal firing. The $GABA_A$ receptor consists of five protein subunits from different classes: α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, π, ρ_{1-3}. In synapses of mature individuals, $GABA_A$ is usually formed by two α_1, two β_2 and one γ_2 subunits, with these being the most abundant subtypes in the adult brain[6].

Metabotropic $GABA_B$ receptors are present in pre- and postsynaptic membranes. When GABA binds to the presynaptic $GABA_B$ receptors, Ca^{2+} conductance is altered, influencing neurotransmitter release. The postsynaptic $GABA_B$ receptors can lead to increased conduction and neuronal hyperpolarisation. The $GABA_B$ receptor consists of two subunits: 1 and 2-t[Error! Bookmark not defined.]. The $GABA_B$ receptor has been shown to be of importance in mediating the interhemispheric inhibition (the inhibition of the responsiveness of the contralateral hemisphere by the active one) in the somatosensory cortex of the mouse[7] and the human primary motor cortex[8].

GABAergic inhibition (regulated through $GABA_B$ and $GABA_A$ receptors) plays a role as well in short-term intracortical inhibition (SICI) and in long-interval intracortical inhibition (LICI). LICI and SICI are cortico-cortical inhibitions taking place in the ipsilateral cortex, and arise in the motor cortex when a conditioning stimulus is presented before a motor cortex test stimulus, inhibiting the motor-evoked potentials[9]. $GABA_B$ receptor-mediated inhibition contributes to LICI, while $GABA_A$ receptor-mediated inhibition occludes LICI[10].

GABA is important as well during development, modulating neuronal maturation and migration and later orchestrating neural oscillation and synchronisation. This synchronised activity is essential for synaptic wiring and neural circuit refinement. In immature neurons, GABA has a depolarizing action instead of the hyperpolarizing action it acquires in mature neural tissue. This is due to the differences in Cl^- concentration in neurons. During development, the Cl^- concentration within neurons is higher because of a decreased expression of the K^+/Cl^- co-transporter (KCC2), which

regulates the outwards flow of Cl^- ions, and an increased expression of the $Na^+/K^+/Cl^-$ co-transporter (NKCC1), which regulates the inwards flow[11]. When GABA binds to postsynaptic $GABA_A$ receptors in these conditions, there is a net outflow of Cl^- ions instead of an inflow, resulting in a membrane depolarisation. The shift from depolarisation to hyperpolarisation is caused by a decrease in Cl^- concentration in neurons[5]. The depolarising action of GABA probably occurs during the first postnatal weeks, and is thought to be essential for the integration of neuronal networks and circuits[12], as well as a trophic/growth-promoting factor[11]. The KCC2 expression is upregulated and the NKCC1 expression is downregulated during neuronal maturation in the first year of life[13]. This leads to the shift from the depolarising (excitatory) to the hyperpolarising (inhibitory) action of GABA[11].

The ratios of GABA/glutamate in the brain are important for the establishment of a neural excitation/inhibition balance[14]. Neurotransmitter synthesis, release, reuptake and breakdown need to work in a coordinated manner in order to keep an appropriate neural transmission[15].

The activity of the GABAergic system in the brain can be measured in different ways. This can be done through genetic observations, *in vitro* post-mortem brain tissue analysis, and *in vivo* brain studies[5]. Genetic analysis can reveal affected genes that have an influence on transcription of GABA receptors. The level of expression of GABA receptors and GAD_{67} and GAD_{65} enzymes in *in vitro* brain tissue can inform on the amount of GABAergic transmission in certain areas of the brain. *In vitro* analysis also allows an investigation of the neuronal structure and eventual anatomical abnormalities in the brain. Detecting and describing the activity of the GABAergic system *in vivo* is more challenging, but there are various available techniques. Proton magnetic resonance spectroscopy (MRS) can measure GABA concentrations in the brain[16]. Another technique is single-photon emission computed tomography (SPECT) combined with ^{123}I-iomazenil, a $GABA_A$-benzodiazepine ligand. Measurements of Gamma-band oscillations can also be used as an indirect method for measuring GABA activity. GABAergic interneurons play an important role in the generation of these high-frequency oscillations and through negative feedback inhibition of principal cells, and are critical for multisensory integration[17].

Abnormalities in the GABAergic system and the excitation/inhibition balance have been found in many neurodevelopmental disorders, particularly in autism spectrum disorder (ASD). The aim of this paper is to describe the current knowledge of GABAergic system abnormalities in ASD and investigate the role of GABAergic signalling in altered sensory processing in individuals with ASD.

GABAergic system in ASD

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication, and repetitive and restrictive behaviours, interests, and activities[18]. Altered sensory perception is present as well in most of the cases[19]. This disorder is diagnosed in early childhood and persists the whole lifetime. It's a heterogeneous condition, with ASD being an umbrella term that includes autistic disorders, Asperger's disorder, childhood disintegrative disorder and pervasive developmental disorder, not otherwise specified (PDD-NOS). Children diagnosed with ASD fall on the autism spectrum, where symptom severity may vary widely between individuals. The population prevalence is close to 1% worldwide, and it is more common in male than in female children[20]. There is a rise in prevalence of ASD over time, and some of the proposed explanations

include the broadening of the diagnostic criteria and the increased efficiency in the identification of cases of ASD[20]. The aetiology of ASD is complex and multifactorial, with interactions between genetic, epigenetic and environmental factors that are not well understood[21]. ASD has a high heritability, ranging from 0.5 to 0.9, but most cases are idiopathic[1]. Around 25% of the individuals with ASD show comorbidity with epilepsy, and individuals with this comorbidity showed lower intellectual, language and speech abilities compared to individuals without epilepsy[22]. This comorbidity provides more indication of a problem in the GABAergic signalling pathway, as GABA plays a role in the development of epilepsy as well[23]. There are many reports of altered GABAergic transmission and excitation/inhibition imbalance in individuals with ASD. This has led to the postulation of the hypothesis that the development of ASD is caused by an excitation/inhibition imbalance, most likely arising from abnormalities in GABAergic transmission.

ASD has a complex genetic background. There are some single nucleotide polymorphisms (SNPs) and chromosome linkage regions that have been causally associated with ASD emergence, and de novo copy number variation involving microduplication or microdeletion have also been linked to a fraction of ASD cases[24]. Genes that have been found to be connected to ASD are SHANK1-3[25,26], NLGN1, NRXN1 and PTCHD1[27]. Nevertheless, these genes are only present in a small number of individuals. Much remains unknown about the genetic underpinnings of ASD[27]. Notably, microduplications in the chromosome 15q11-q13 region have been associated with ASD (0.5%) in some studies[1,24,28]. This region includes the genes for $GABA_A$ receptor subunits GABARB3, GABARA5, and GABARG3, further emphasizing the possible role of the GABAergic system in the development of ASD.

Cellular abnormalities in anatomical structures of the brain that are involved in the control of excitation and inhibition have been identified in individuals with ASD[14]. The expression of $GABA_A$ receptors has been found to be reduced in the superior frontal cortex, parietal cortex and cerebellum[29]. $GABA_B$ receptors have been found to show a decreased density as well in the frontal and parietal cortex[30]. Dysregulations in GABA metabolism have also been found, indicated by a reduction in the protein levels of GAD_{67} and GAD_{65} in parietal and cerebellar areas of individuals with ASD[31], combined with a decreased level of GAD_{67} mRNA expression in Purkinje cells[32]. All these abnormalities suggest a decrease in inhibitory function in individuals with ASD.

GABA levels have been found to be decreased in the frontal lobe[33] and auditory cortex of individuals with ASD[34], supporting the theory of a decreased inhibitory function. Plasma levels of GABA, on the contrary, seem to be elevated, while the excitatory neurotransmitter glutamate (Glu) is slightly decreased, resulting in a reduced Glu/GABA ratio and confirming an abnormal glutamate/GABA cycle[35]. These elevated GABA plasma levels can be associated with the decreased cortical GABA levels because of lower GABA receptor numbers in the brain.

Cortical minicolumns (columns of pyramidal cells that are the smallest neocortical modules for information processing[36]) have been found to be altered in ASD as well. Minicolumns are surrounded by GABAergic inhibitory interneurons, and it has been postulated that a narrower minicolumn width could indicate an increased inhibition[15]. Nevertheless, the results are not consistent, with some researches reporting a decreased minicolumn width[37] and some an increased minocolumn width[38] in different brain regions.

Alterations in KCC2 and NKCC1 have been found in ASD and models of genetic disorders that are strongly associated with autism. Rare KCC2 variants have been found in individuals with ASD, suggesting an epigenetic dysregulation of KCC2[39], pointing at an altered excitatory-inhibitory shift of GABA action. The GABA shift has been found to be delayed in mice with fragile X syndrome (FRX) and in rats exposed to valproate (VPA) *in utero*[40]. Chloride export has been found to be reduced as well in both rodent models[41], causing longer excitatory GABA action in newborn and juvenile neurons and hyperactive developing networks that produce long-term effects in juvenile rodents. In addition, oxytocin, an important hormone in the regulation of social behaviour, appears to play an important role in the GABA shift by modulating the developmental increase of KCC2[42]. All these studies show that the shift in GABA action seems to occur at a later time in ASD, probably altering neuronal circuit formation and resulting in the ASD behavioural phenotype.

GABAergic system and sensory processing

The GABAergic system is essential for the regulation of neuronal activity levels, neuronal plasticity, the generation of neuronal oscillations, and the control of the size and propagation of neuronal assemblies through the inhibition of neuronal networks[12]. GABA has an important role as well in cognition and memory[43], sleep state regulation[44], and control of executive functions[45] and anxiety[46].

On a structural level, according to the minicolumn model[36], the somatosensory cortex is organised in minicolumns, where GABAergic double-bouquet cells inhibit neighbouring minicolumns[47]. Sensory stimuli activate a complex pattern of activity in cortical minicolumns; abnormalities in GABAergic neuron function could lead to minicolumn structure changes, causing an imbalance between excitation and inhibition and, as a consequence, giving rise to abnormalities in sensory processing.

GABAergic system and sensory processing in ASD

Sensory perception anomalies and sensory processing abnormalities are common in ASD and are included as a core diagnostic feature in the DSM-V criteria for ASD[48]. Around 90% of children with ASD show sensory abnormalities and have sensory symptoms in multiple sensory domains including touch, smell/taste, pain, audition and vision, which persist across age and IQ[49]. These sensory abnormalities are present already at six months of age[50], preceding and predicting communicative-social deficits[51]. Because of the role of GABAergic inhibitory function in sensory processing, it is of importance to investigate the abnormalities in GABAergic expression and transmission in sensory processing of different modalities of sensory input in individuals with ASD. This will provide more information on the neurobiological basis of sensory processing abnormalities in ASD and will help support or discredit the theory of excitation/inhibition imbalance as causation of the development of ASD.

Visual stimuli

Visual abnormalities in ASD have been widely described, with individuals seeking or avoiding intense visual stimulation[52]. Perceptual processing of visual information is altered in ASD, with individuals focussing on details over global features of a sensory scene[53]. This is indicated by a superior visual search performance compared to neurotypical individuals regardless of the number of stimuli that are presented simultaneously in adults with ASD[54]. Individuals with ASD thus seem to be better at discriminating multiple visual stimuli at an early level of processing. Gaze-tracking has shown that adult individuals with ASD have a high preference for pixel-level saliency (colour, intensity and

orientation) regions in a scene, a lower object-level saliency (size, complexity, solidity) preference compared to neurotypical individuals and a stronger image-centre bias[55]. This corroborates that individuals with ASD have detail-focussed visual preferences. Nevertheless, the reason for this high attention to detail and enhanced discriminating abilities still remains to be found[53], as other basic visual sensitivity measures such as visual acuity[56] and contrast discrimination[57] have been found to be typical. A reduced saliency for faces has also been detected[55], as well as a less accurate recognition and differentiation of emotional facial expressions[58].

Individuals with ASD have an atypical processing of dynamic stimuli[59], with difficulties in global motion perception[60]. It takes longer to process global orders, especially if there are incongruences on a local level, suggesting a local-to-global interference in individuals with ASD[61]. However, when briefly-presented high-contrast moving stimuli were shown, individuals with ASD demonstrated an enhanced capacity to perceive direction, suggesting abnormal contrast gain control and supporting the hypothesis of altered excitation/inhibition balance[62].

Some studies show visual processing abnormalities in children with ASD without any differences in occipital GABA levels, showing an absence of correlation between GABA and visual processing in ASD[63]. Other studies have linked a decrease in GABA concentrations in the visual cortex to a deficit in binocular rivalry (dependent on inhibitory strength) in ASD[64], and have found a decreased gamma oscillation in visual areas when individuals with ASD were presented with visual stimuli[65], suggesting an impaired excitation/inhibition balance.

The GABAergic system abnormalities and sensory perception anomalies present in ASD could impact the social domain of the ASD symptomatology. The preference for detail over global in visual information processing and the impairments in perceiving certain visual characteristics could lead to the poorer facial and emotional identification, reduced facial saliency and global motion in ASD, which are essential in the social and cognitive development. Especially altered biological motion detection (the movements of humans and other animals), crucial in the development of imitation, emotion recognition, joint attention and social cognition in general, could cause a great part of the social impairments present in ASD[52].

Tactile stimuli

Research regarding responses to tactile stimulation in ASD shows mixed results, with documented hypo- and hyper-reactivity to tactile stimuli[52]. Adaptation to tactile stimulation has been found to be reduced in individuals with ASD, suggesting a functional deficit in the somatosensory inhibitory system[66]. Reduced sensorimotor GABA levels *in vivo* have been found to be associated with abnormalities in tactile performance in children with ASD, suggesting that the GABAergic system may be responsible for the abnormal tactile information processing[63]. The threshold for static vibrotactile stimuli has been shown to be higher in children with ASD compared to neurotypical controls, with a higher threshold correlating with more severe ASD symptoms[67]. Vibrotactile tests rely partly on cortical GABAergic inhibitory mechanisms[47], and the difference between thresholds for static and dynamic stimuli predicts GABA mediated feed-forward inhibition[68]. A lower ratio between dynamic and static vibrotactile thresholds has been demonstrated in ASD, suggesting a reduced GABA mediated feed-forward inhibition, which was further diminished when ASD symptomatology was more severe[67]. GABA levels in the sensorimotor cortex (measured with MRS) have been found

to be reduced as well, linking GABAergic system abnormalities in the brain to impaired tactile performance[63].

Touch is important in the development of social bonds and communication. The impairments in tactile processing and evidence of a reduced GABAergic inhibition found in ASD alter touch-seeking behaviour, affecting social interactions and development of emotional attachments[52].

Auditory stimuli

Abnormal auditory processing in ASD has been widely reported[53,69]. Some children with autism (but not Asperger syndrome) show an enhanced pure-tone pitch perception[70], but this is less present during adolescence, where only 20% of the individuals with ASD showed exceptional pure-tone pitch perception that was associated with language delay[71]. Enhanced loudness sensitivity has been found in a subgroup of individuals with ASD and seems to decline with age[53]. Adults with ASD have shown a diminished auditory stream separation, which leads to difficulties in selectively separating relevant sounds in a noisy environment[72]. These deficits in the filtering of auditory information suggest an abnormal auditory integration[52]. Children with ASD show an impaired orientation to social auditory stimuli and a decreased attention[73].

Results of different studies show that GABA levels, measured with MRS, are decreased in the auditory areas in children with ASD[34,74]. These lower GABA levels in ASD have been linked to a decreased gamma band activity[75], demonstrating that GABA abnormalities are present as well in auditory processing.

Abnormal auditory processing, possibly due to underlying GABAergic abnormalities, has an impact on social interaction and communication. The lack of the ability to focus on specific auditory cues hints towards an excitation/inhibition imbalance and may result in a decreased capacity to direct attention to auditory stimuli containing social information, such as speech. This has a direct impact on social engagement. In addition, individuals with ASD show speech-related auditory impairments[76], contributing to language development deficits. Impairments in the detection of emotionally-laden speech have been found as well[77], affecting social reciprocity[52].

Olfaction and gustation in ASD have been investigated relatively less compared to vision, audition and touch. There have been accounts of abnormal taste detection[78], enhanced olfactory sensitivity[79], and problems with odour identification[80], but there has been little research on the role of the GABAergic system in these sensory modalities.

GABAergic abnormalities do not only appear to affect sensory processing in ASD. In rodent models, repetitive behaviours such as self-grooming and circling have been linked to GABAergic alterations, where GABA receptor agonists reduced repetitive self-grooming in mice models and induced circling behaviour in healthy rats[81]. It has been suggested that repetitive behaviours are associated with imbalance of cortico-striatal circuits, possibly through reduced GABA-mediated inhibition[82].

Sensory abnormalities predict social-communication deficits and repetitive behaviours in childhood[53]. Hyper-responsiveness to sensory stimuli has been found to be associated with repetitive behaviours and correlated to stereotypy in ASD, suggesting that shared neurobiological mechanisms may exist between abnormal sensory processing and repetitive behaviours[83]. This indicates that sensory processing and GABAergic abnormalities are not a separate domain in ASD,

but rather suggest an interplay with socio-communicative skills and repetitive/stereotypical behaviours that gives rise to the behavioural phenotype of ASD.

Conclusion

There are numerous indications that GABAergic signalling is altered in ASD, related to the sensory modalities of vision, audition and tactile processing. Most studies investigating the role of the GABAergic system in visual, auditory and tactile processing found abnormalities in GABAergic inhibition. These findings, combined with behavioural results that indicate a deficit in information filtering, suggest an abnormal inhibition. Overall, the results seem to support the hypothesis of an altered excitation/inhibition balance in ASD, in which the GABAergic system plays a crucial role. However, the results and findings concerning GABAergic processing in ASD are mixed and it's not clear whether there is a reduced or an increased inhibition. Some researchers have found a reduced amount of the GABA neurotransmitter[33,34], or a decrease in the expression of GABA receptors[29,30] in different brain areas, suggesting a reduced GABA-mediated inhibition. Other studies, nevertheless, discovered contrasting evidence that hinted at an increase in GABA-mediated inhibition[38]. Sensory processing and GABAergic abnormalities have been linked to the other core domains of ASD, the socio-communicative impairments[52] and repetitive/stereotypical behaviours[83], suggesting that the different aspects of the ASD behavioural phenotype may share a common neurobiological basis and influence each other. The delay in the switch in GABAergic transmission from excitatory to inhibitory seen in ASD may have a great effect on neural network organisation, possibly affecting sensory processing and circuits involved in social and language development.

One plausible explanation for the conflicting results concerning GABAergic transmission is the fact that ASD is a very heterogeneous condition, with severity of symptoms and symptomatology differing greatly between individuals. The age of the children with ASD also plays an important role, as symptom severity seems to modestly decrease as the age of the children increases[84]. Even taking into account that most of the subjects in the discussed studies were high-functioning individuals with ASD, the differences in the subject pool between researches was possibly very high. In addition, only a fraction of individuals with ASD shows mutations in GABA-related genes or comorbidity with epilepsy indicating a GABAergic system dysfunction, suggesting that at least a part of the individuals with ASD may have a more affected GABAergic system than others. The delay in the switch of the action of GABA from excitatory to inhibitory may also differ between individuals, with different consequences for neural circuitry development, leading to individual differences in the GABAergic pathway and accounting for heterogeneity in ASD.

Another issue to take into consideration is that different studies measured GABAergic parameters in different anatomical regions of the brain. It is possible that the GABAergic pathway and GABAergic transmission in ASD are only affected in certain areas of the human brain during certain tasks: some parts may show an increased inhibition, while others may show a decreased inhibition in response to different stimuli.

It is necessary that these issues are considered when evaluating and comparing different studies. In many occasions, it is a possibility that the results of a study are only applicable to the subgroup of individuals with ASD with similar symptoms as the subgroup sampled by the study itself. Therefore, one has to be very careful when applying the conclusion of a single research to the whole autism

spectrum. Instead of combining all findings and making generalised conclusions about the whole spectrum, a comparison of ASD subgroups could be insightful in investigating GABAergic abnormalities.

Little research has been conducted to describe the role of the GABAergic system in the processing of olfaction and gustation in ASD. Some abnormalities in these domains have been described, but a more extensive study of the neurobiological underpinnings of these sensory abnormalities could help developing a better understanding of sensory processing in ASD.

Finally, further research regarding the effects of the GABAergic system and sensory processing on the development of social and communication deficits, and stereotypical/repetitive behaviour may help understand the complexity of the neurobiological basis of ASD.

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