Brain Research 1648 (2016) 277–289

Contents lists available at ScienceDirect

Brain Research

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

Review

Measuring neural excitation and inhibition in autism: Different approaches, different findings and different interpretations

Abigail Dickinson *, Myles Jones, Elizabeth Milne *

Department of Psychology, University of Sheffield, Western Bank, Sheffield S10 2TP, UK

ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form
23 June 2016
Accepted 11 July 2016
Available online 12 July 2016

Keywords:
Autism
Excitation/inhibition
GABA
Glutamate

ABSTRACT

The balance of neural excitation and inhibition (E/I balance) is often hypothesised to be altered in autism spectrum disorder (ASD). One widely held view is that excitation levels are elevated relative to inhibition in ASD. Understanding whether, and how, E/I balance may be altered in ASD is important given the recent interest in trialling pharmacological interventions for ASD which target inhibitory neurotransmitter function. Here we provide a critical review of evidence for E/I balance in ASD. We conclude that data from a number of domains provides support for alteration in excitation and inhibitory neurotransmission in ASD, but when considered collectively, the available literature provide little evidence to support claims for either a net increase in excitation or a net increase in inhibition. Strengths and limitations of available techniques are considered, and directions for future research discussed.

Contents

1. Introduction

Autism spectrum disorder (ASD) is diagnosed based on the presence of impairments in social interaction and communication, accompanied by restricted and repetitive behaviours (American Psychiatric Association, 2013). ASD has been reported to affect around 1 in 68 children (Christensen, 2016), yet the precise etiology of the condition is unknown. One hypothesis regarding the pathophysiology of ASD centres on alteration in the balance of neural excitation and inhibition (E/I balance), which is mediated by the effective magnitude and timing of excitatory and inhibitory

* Corresponding authors.
E-mail addresses: abbydickinson317@gmail.com (A. Dickinson), e.milne@sheffield.ac.uk (E. Milne).

http://dx.doi.org/10.1016/j.brainres.2016.07.011
0006-8993/

synaptic inputs to a cortical neuron or network. Due to the widespread consequences that altered E/I balance has for brain function and behaviour (Haider et al., 2013), E/I imbalance has been suggested as a possible explanation for the behavioural, cognitive and perceptual differences observed in those with ASD. While most accounts suggest that excitation may be increased relative to inhibition in ASD (Coghlan et al., 2012; Hussman, 2001; Markram et al., 2007; Rubenstein and Merzenich, 2003), others suggest that inhibition may be increased in ASD relative to excitation (Bertone et al., 2005; Gustafsson, 1997a). When evaluating the diverse results of studies which assess E/I balance in ASD, one thing which should be considered is the possibility that an imbalance (or the direction of such imbalance) may not manifest in a ubiquitous way across the condition. ASD is highly heterogeneous, and likely emerges as the consequence of diverse neurobiological sequelae, as is suggested by the many different genetic abnormalities associated with ASD (Miles, 2011). It is therefore possible that sub-groups of individuals with ASD have specific differences in E/I balance that are not universal, and may contribute to the heterogeneity of the condition.

The suggestion that E/I balance is altered in ASD, and in particular the hypothesis that excitation is increased relative to inhibition in ASD, is largely based on the observation that seizure disorders such as epilepsy frequently co-occur with ASD (Rubenstein and Merzenich, 2003). Estimates of the prevalence rates of epilepsy in ASD range from 5% to 46% (Bryson et al., 1988; Hughes and Melyn, 2005) and converge at around 30% (Canitano, 2007). Subclinical epileptiform activity in the electroencephalography (EEG) is also present in a high proportion of children with ASD (Chez et al., 2006; Hughes and Melyn, 2005; McVicar et al., 2005; Rossi et al., 1995) with one study suggesting that up to 85% of children display such activity (Yasuhara, 2010). However, epilepsy does not arise simply due to an increase in neuronal excitation or decrease in inhibition (Engel, 1996) and seizures occur as a result of complicated neuronal interactions that can differ both within and between patients. In addition, not all individuals with ASD have co-occurring seizures, and not all individuals with epilepsy have ASD. This suggests that there may be different neural pathways to the symptoms of ASD, and that the neural changes associated with epilepsy do not necessarily lead to ASD. It also highlights the importance of obtaining data that directly measures E/I balance in ASD.

Over the last decade, myriad research papers from a range of disciplines have attempted to test the hypothesis that E/I balance is altered in ASD. Examples include: studies that measure gamma-Aminobutyric acid (GABA) and glutamate (the main inhibitory and excitatory neurotransmitters) receptors in post-mortem brain tissue (e.g. Fatemi et al., 2009); studies that use Magnetic Resonance Spectroscopy (MRS) to measure GABA and glutamate levels in vivo (e.g. Rojas et al., 2014), and studies that measure aspects of perception from which alterations in E/I balance are inferred (Dickinson et al., 2016, Robertson et al., 2015). A number of excellent methodologically-specific review articles evaluating some of this work have been published recently. For example Rojas et al. (2015) reviewed MRS studies that measure glutamate and GABA levels in ASD, and Pizzarelli and Cherubini (2011) reviewed cellular abnormalities that implicate E/I imbalance in animal models of ASD (see also Coghlan et al. (2012)). Here we take a broader approach, and rather than focusing on data arising from a specific technique or field, we review data arising from the range of methodologies that have been used to investigate, or infer, E/I balance in ASD.

2. Empirical evidence for E/I imbalance in ASD

We start the review with a description of neuro-architectural differences associated with E/I imbalance in ASD, including cellular abnormalities measured from post-mortem brain tissue and minicolumnar structure. We then consider studies that measure excitatory and inhibitory neurotransmitters, from both blood plasma and brain, before describing how differences in gamma-band activity recorded by magnetoencephalography (MEG) or EEG, and atypical perceptual function, have been considered to infer E/I imbalance in ASD. An emerging theme from this review is that measuring E/I balance in humans is not straightforward. Many of the claims made regarding altered E/I balance in ASD rely on assumptions, such as assumptions about how alteration of one feature, such as cortical neurotransmitter levels or synaptic protein levels may affect net E/I balance, or assumptions about the extent to which a certain perceptual task reflects E/I balance. Nevertheless, the collective findings from this body of work certainly imply that E/I balance may be disrupted in ASD, although we would argue that the strength of available evidence is not sufficient to accurately describe the direction of such an imbalance (i.e. whether excitation is increased or reduced relative to inhibition).

2.1. Cellular abnormalities

Arguably, the most compelling evidence for altered E/I balance in ASD comes from studies that have identified abnormalities in anatomical features that are associated with controlling neural excitation and inhibition in ASD. Although many cellular abnormalities have been reported in ASD, this discussion will only highlight examples of the cellular abnormalities found in ASD that are considered to implicate E/I balance (for a more thorough review and diagram of E/I balance at a cellular level, see Coghlan et al. (2012)). See Table 1 for a summary of the studies described in this section.

Neural transmission relies on a complex system of neurotransmitter generation, release, reception and re-uptake. In ASD, abnormalities have been found in many of the components of this system. For example Fatemi et al. (2009) found reductions in $GABA_A$ receptor density in parietal, cerebellar and superior frontal regions in ASD (see also Blatt et al. (2001), Fatemi et al. (2009, 2014), Oblak et al. (2011, 2010, 2009)), and AMPA-type glutamate receptor density was found to be reduced in the cerebellum of individuals with ASD (Purcell et al., 2001). There is also evidence that the synthesis of GABA and glutamate is altered in ASD. Glutamic acid decarboxylase (GAD) is an enzyme responsible for catalysing the decarboxylation of glutamic acid to form GABA and exists in two isoforms: 65 and 67 (GAD65; GAD67). Post mortem studies have revealed that both GAD65 and GAD 67 are decreased in the cerebellum and parietal cortex of individuals with ASD (Fatemi et al., 2002; Yip et al., 2007). In addition, Shimmura et al. (2013) found that enzymes associated with the glutamate-glutamine cycle are decreased in post mortem brain tissue of individuals with ASD, thus also suggesting a dysfunction in excitatory neurotransmission in ASD.

These studies provide strong evidence for the position that E/I balance is likely to be altered in ASD, however, it is hard to predict how a disruption in either receptor density and / or enzyme levels would affect overall E/I balance in ASD. For instance, low levels of GABA receptor expression may be compensated for by higher levels of GABA being released from presynaptic terminals (Dhossche et al., 2002; Fatemi et al., 2009). Therefore, while this research strongly implicates alteration in mechanisms underpinning E/I balance in ASD, it does not speak clearly to the direction of such an imbalance. Numerous animal models that mimic some aspects of the behavioural symptoms of ASD also display alterations in E/I balance, with altered GABAergic and glutamatergic transmission observed in several studies (for a review see Pizzarelli and Cherubini (2011)). However, whilst Markram et al. (2008) find defective inhibitory transmission in one mouse model of ASD, other models