Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Potential synergistic action of 19 schizophrenia risk genes in the thalamus

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ARTICLE INFO

Article history:
Received 17 May 2016
Received in revised form 31 August 2016
Accepted 3 September 2016
Available online xxxx

Keywords:
Schizophrenia
NMDAR hypofunction
Dopamine receptor hyperfunction
Delta oscillations
Nucleus reticularis
Relay cells

ABSTRACT

A goal of current schizophrenia (SZ) research is to understand how multiple risk genes work together with environmental factors to produce the disease. In schizophrenia, there is elevated delta frequency EEG power in the awake state, an elevation that can be mimicked in rodents by *N*-methyl-D-aspartate receptor (NMDAR) antagonist action in the thalamus. This thalamic delta can be blocked by dopamine D2 receptor antagonists, agents known to be therapeutic in SZ. Experiments suggest that these oscillations can interfere with brain function and may thus be causal in producing psychosis. Here we evaluate the question of whether well-established schizophrenia risk genes may interact to affect the delta generation process. We identify 19 risk genes that can plausibly work in a synergistic fashion to generate delta oscillations.

1. Introduction

It is now widely accepted that there is both environmental and genetic causation of schizophrenia (SZ). Risk genes for SZ have been identified by copy number variations (CNVs) (Walsh et al., 2008; Kirov et al., 2011) or single-nucleotide polymorphisms (SNPs) (Ripke et al., 2014). Importantly, the effect size of each gene is small, meaning that the presence of a risk gene in an individual only marginally increases the risk of the disease. It is therefore generally supposed that the disease itself requires the concerted action of many risk genes on some critical brain process. What might that critical process be and what is the nature of the interaction?

One possible answer comes from another line of investigation that has sought to understand a well-established symptom of schizophrenia: the elevation of low-frequency (delta; 1–4 HZ and theta; 4–7 Hz) EEG oscillations in the awake state (here termed simply "delta") (Clementz et al., 1994). A number of studies have identified increased delta in both medicated and unmedicated SZ patients, primarily in the temporal and parietal areas and generally bilateral (Fehr et al., 2001, 2003; Wienbruch et al., 2003; review in Siekmeier and Stufflebeam, 2011). This increase is not seen in first-degree relatives of SZ patients (Venables et al., 2008). Furthermore, significant correlations have been found between the increase in delta power and both positive (Fehr et al., 2001) and negative symptoms of SZ (Fehr et al., 2003).

Insights into the network basis of the delta abnormality have been gained using the NMDAR hypofunction model of the disease (Coyle, 1996; Javitt and Zukin, 1991), a model justified by the fact that NMDAR antagonists can reproduce many of the positive, negative, and cognitive symptoms of the disease (see (Moghaddam and Krystal, 2012)). Notably, NMDA antagonists can elevate low-frequency oscillations in rodents and man (Buzsáki, 1991; Zhang et al., 2012b). Importantly, the work in animal models has identified the thalamus as the site where NMDAR antagonists produce delta (Buzsáki, 1991; Zhang et al., 2012b), and much has been learned about the underlying cellular and molecular processes (Lisman et al., 2010; Zhang et al., 2009, 2012a, b). Furthermore, optogenetic experiments have established that the induction of abnormal delta oscillations in a particular thalamic nucleus (reuniens) is sufficient to interfere with cognitive function (Duan et al., 2015). Specifically, the results show that optogenetic stimulation at delta frequency interfered with spatial working memory, an established function of the nucleus reuniens and a function known to be affected in schizophrenia. While elevated delta activity is also seen in several other disorders (Knyazev, 2012), it has been proposed (Schulman et al., 2011) that low-frequency oscillations can occur in different parts of the cortex and the associated thalamic nuclei, with the presentation of particular symptoms depending on the functions of the thalamic nuclei affected. Thus different symptoms (positive/negative/cognitive) of schizophrenia could potentially relate to which thalamic nuclei are involved.

Given that abnormal delta in the thalamus might be the critical process affected in schizophrenia, it becomes important to consider whether identified risk genes could act together to produce abnormal delta. In this brief review, we seek to evaluate this possibility. Fig. 1 shows the

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http://dx.doi.org/10.1016/j.schres.2016.09.008
0920-9964/

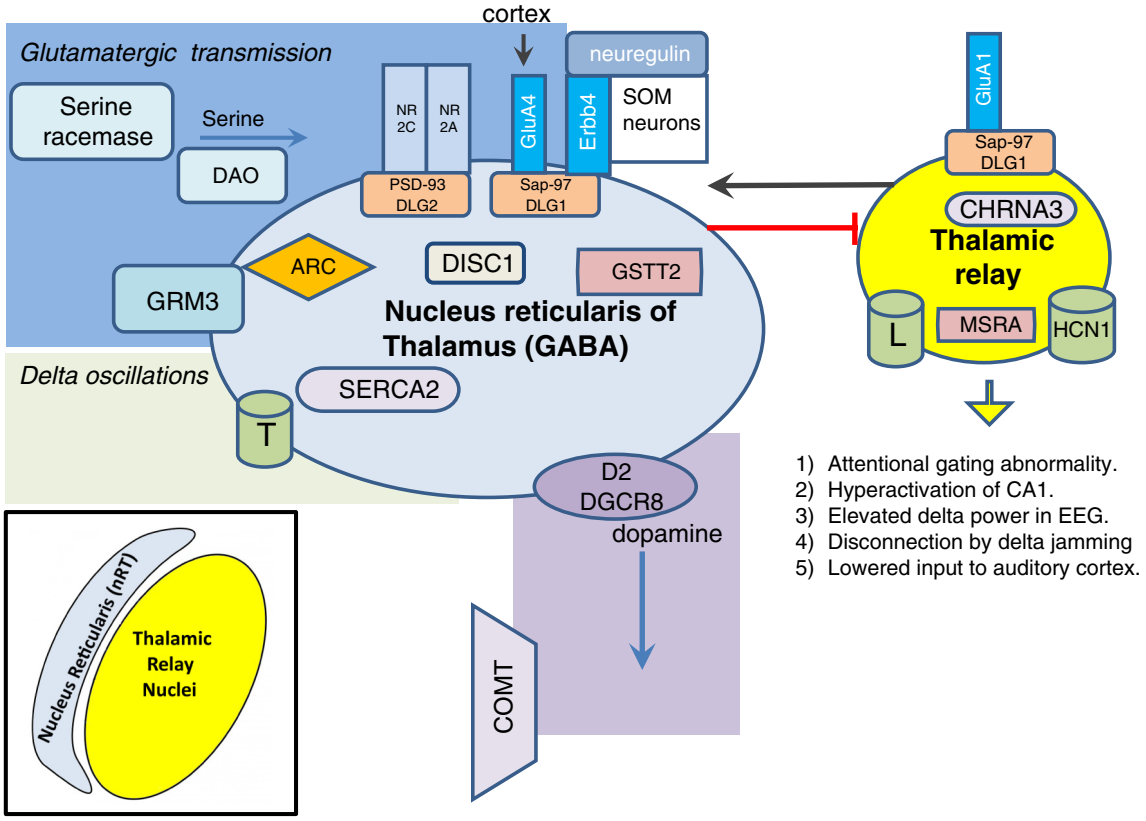

Fig. 1. Nineteen risk genes for schizophrenia may affect delta generation in the thalamus. In the thalamus, inhibitory cells of the nRT interact with excitatory relay cells of thalamic nuclei. For ease of visualization, risk genes that affect glutamatergic function (NMDA hypofunction), dopamine hyperfunction, and delta generation are placed against different background colors. The lower-left inset shows the layout of the nRT. Genes are 1) *T* T-type calcium channel (CaV3.3); 2,3) *L* L-type calcium channel (CaV1.2 alpha subunit or CaVB2 beta subunit); 4) *SERCA* sarcoplasmic/endoplasmic reticulum Ca transporting ATPase (ATP2A2); 5) *HCN1* hyperpolarization-activated, cyclic-nucleotide gate K channel 1 (HCN1); 6) *GRM3* glutamate receptor metabotropic 3; 7) *D2* dopamine receptor D2 (DRD2); 8) *DGCR8* DiGeorge critical region 8; 9) *COMT* catechol-*O*-methyl transferase; 10) *Serine racemase* (SRR); 11) *GSTT2* glutathione-S-transferase theta 2; 12) *MSRA* methionine sulfoxide reductase A; 13) DISC1 disrupted in schizophrenia 1; 14) *ARC* activity-regulated cytoskeleton-associated protein; 15) *GluA1* glutamate ionotropic AMPA receptor 1 (GRIA1); 16) *Erbb4* erb-b2 receptor tyrosine kinase 4; 17) *SAP-97* synapse-associated protein 97 (DLG1); 18) *PSD-93* postsynaptic density protein 93 (DLG2); 19) CHRNA3 Cholinergic receptor nicotinic alpha 3 subunit. Also shown are GluA4, DAO, NR2C and NR2A, which are relevant to thalamic function, but have not been strongly implicated in the disease by genetic studies. *DAO* D-amino acid oxidase; *GluA4* glutamate ionotropic AMPAR subunits; *NR2A or NR2C* glutamate ionotropic NMDA receptor subunits; neuregulin is shown in this figure because of its role in the control of thalamic function (Ahrens et al., 2014). *SOM* somatostatin interneuron. The list at bottom right gives the symptoms of SZ that may be linked to thalamic dysfunction in SZ: attentional gating (Behrendt, 2003), hyperactivation of CA1 (Schobel et al., 2009; Zhang et al., 2012b), elevated delta power (Clementz et al., 1994), delta jamming (Duan et al., 2015), and lowered auditory input (Chun et al., 2014). Note that the proportions in this figure do not reflect the actual sizes of the nRT and thalamic relay nuclei. Also note that, while some of these genes displayed in the nRT are also present in relay nuclei, and vice versa, we only show where the genes are preferentially expressed.

two cell types of the thalamus most relevant to delta generation, the inhibitory cells of the nucleus reticularis (nRT) and excitatory cells of relay nuclei. Relay cells excite the cells of the nRT, which in turn inhibit the relay cells. Although individual cells can themselves be oscillatory, thalamo-cortical oscillations are ultimately a network process to which both excitatory and inhibitory cells of the thalamus contribute (Crunelli et al., 2014). Delta oscillations, which are accompanied by bursting in a large fraction of cells in the thalamus (Crunelli et al., 2014), may interfere with the function of affected thalamic nuclei by jamming the normal transmission of information through the nuclei (Duan et al., 2015), thereby potentially contributing to the functional disconnection of cortical regions in SZ (Schulman et al., 2011).

The number of genes for which there is some evidence of linkage to SZ is enormous, but the statistical power of the linkage is often weak. Therefore, in our attempt to understand gene interactions, we have focused on a few studies that are particularly strong; we have considered only genes identified by one or more of the three approaches described below.

The most common method to identify risk genes is to do a genome-wide association study (GWAS) of SNPs, comparing patients and normal controls. The regions around each SNP (risk locus) are then evaluated to identify risk genes or regulatory sequences. We have used the list of 108 risk loci identified or confirmed by the Schizophrenia Working Group of the Psychiatrics Genetics Consortium in 2014 (Ripke et al., 2014), the largest such study. The consortium drew from a pool of 36,989 patients with schizophrenia and 113,075 controls.

An independent approach has been to apply multivariate association analysis between EEG and SNPs. A group of risk genes was thereby directly linked to the increased delta frequency power found in patients with schizophrenia (Narayanan et al., 2015).

As a third source of strongly implicated risk genes, we drew from several studies that focused on identifying the genes associated with large (>100 kb) duplications or deletions of DNA, CNVs, that were found to confer an increased risk of schizophrenia (Walsh et al., 2008; Kirov et al., 2011; Fromer et al., 2014). Of specific interest is the DiGeorge syndrome deletion at 22q11.2 that carries a 30% risk of schizophrenia. Deletions of this region can be of varying size, but a core deletion (DiGeorge Critical Region) of approximately 1.5 MB containing approximately 30 genes has been identified (Chun et al., 2014; Kobrynski and Sullivan, 2007).

A crucial physiological process that underlies delta generation in the thalamus is the delta frequency Ca spikes generated by T-type Ca channels. Importantly, these channels are themselves regulated by membrane potential. At normal resting potential, these channels are inactivated and delta oscillations are not present. When membrane potential becomes hyperpolarized, the T-type Ca channels become functional (deinactivated) and generate Ca spikes at delta frequency,

Please cite this article as: Richard, E.A., et al., Potential synergistic action of 19 schizophrenia risk genes in the thalamus, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.09.008