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Review Article

NMDAR hypofunction and somatostatin-expressing GABAergic interneurons and receptors: A newly identified correlation and its effects in schizophrenia

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ABSTRACT

This review investigates the association between *N*-methyl-D-Aspartate receptor (NMDAR) hypofunction and somatostatin-expressing GABAergic interneurons (SST+) and how it contributes to the cognitive deficits observed in schizophrenia (SZ). This is based on evidence that NMDAR antagonists caused symptoms resembling SZ in healthy individuals. NMDAR hypofunction in GABAergic interneurons results in the modulation of the cortical network oscillation, particularly in the gamma range (30–80 Hz). These gamma-band oscillation (GBO) abnormalities were found to lead to the cognitive deficits observed in the disorder. Postmortem mRNA studies have shown that SST decreased more significantly than any other biomarker in schizophrenic subjects. The functional role of Somatostatin (SST) in the aetiology of SZ can be studied through its receptors. Genetic knockout studies in animal models in Huntington's disease (HD) have shown that a specific SST receptor, SSTR2, is increased along with the increased NMDAR activity, with opposing patterns observed in SZ. A direct correlation between SSTR and NMDAR is hence inferred in this review with the hope of finding a potential new therapeutic target for the treatment of SZ and related neurological conditions.

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1. Introduction

Schizophrenia (SZ) is a neurodevelopmental disorder afflicting around 26 million people worldwide (Eaton et al., 2008). Its symptoms encompass hallucinations, delusions, social withdrawal and cognitive

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deficits, often emerging in late adolescence or early adulthood (Jadi et al., 2015). Cognitive function impairments are observed in aspects of attention, reasoning, memory and speed processing. Kahn and Keefe (2013) suggested that these cognitive deficits are the core clinical feature of SZ, but their response to current antipsychotic medications is minimal (Keefe and Harvey, 2012).

It is proposed that cortical information when performing cognitive tasks is transferred through synchronous oscillations in the cortical networks. The oscillatory activity varies across different behavioural states and cognitive tasks, showing several frequency bands such as theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–80 Hz) as reviewed by Wang (2010), as well as Uhlhaas and Singer (2010). Gamma band oscillations (GBO) are associated with neural ensemble synchronization during stimulus or task-driven cognitive states such as attention, complex processing of information, working memory and feature binding (Fries, 2009; Lesh et al., 2011; Salinas and Sejnowski, 2001). GBO power is consistently abnormal in SZ when compared to healthy individuals (Gonzalez-Burgos and Lewis, 2008; Jadi et al., 2015; Uhlhaas and Singer, 2010).

According to Lewis (2014), the cognitive deficits of SZ arise from GBO abnormalities, which directly depend on the synaptic inhibitory action of gamma-aminobutyric acid (GABA) interneurons in the brain's cortical circuitry (Buzsáki and Wang, 2012). Thus, cognitive dysfunctions in SZ are suggested to be a result of GABAergic inhibition abnormalities (Lewis et al., 2005).

Furthermore, it is proposed that *N*-methyl-D-aspartate receptor (NMDAR) hypofunction in these GABAergic interneurons is involved in the GBO alteration observed in schizophrenic patients. The NMDAR has attracted interest due to the effects of NMDAR antagonist phencyclidine (PCP) producing SZ-like symptoms in healthy individuals (Luby et al., 1959). Studies have since suggested links between NMDAR hypofunction and SZ (Carlsson and Carlsson, 1990; Olney and Farber, 1995). This was supported by the use of other NMDAR antagonists such as ketamine and MK801 causing a decrease in GABAergic interneurons in animals (Abekawa et al., 2011; Wang, 2010), and behavioural deficits similar to human SZ (Olney and Farber, 1995).

A certain type of cortical GABAergic interneurons is categorised by its expression of a unique molecular marker known as somatostatin (SST) as reviewed by Yavorska and Wehr (2016). SST is co-localized with GABA as an inhibitory neuropeptide with modulatory and inhibitory actions in the brain. It is also involved in the regulation of behavioural and physiological stress responses such as the inhibition of hypothalamic hormone release, cortical circuit integration of sensory input and the amygdala central nucleus output (Lin and Sibille, 2013).

Alterations in somatostatin-expressing (SST+) GABA interneurons are found to be associated with SZ (Morris et al., 2008). SST+ interneurons exert differential inhibitory effects on excitatory neurons in specific layers of the neocortex (Xu et al., 2013). Moreover, SST mRNA levels in the GABAergic interneurons are significantly decreased in the cortices of SZ patients. In fact, SST deficits were also observed in many other human psychiatric and neurological disorders such as major depressive disorder, bipolar disorder, Alzheimer's disease and Parkinson's disease as reviewed and summarized by Lin and Sibille (2013).

Rajput et al. (2011) showed that SST functions as a neuroprotective agent in the central nervous system through acting on five different receptor subtypes(SSTR1-5). When the SSTR1 and SSTR5 genes are knocked out in mice, symptoms resembling Huntington's disease (HD) are generated. This also lead to an increase in SSTR2 to perhaps compensate for the loss of SSTR1 and SSTR5 in order to protect neurons from excitotoxicity caused by the well-established increase in NMDAR activation seen in HD models (Chen et al., 1999; Fan and Raymond, 2007; Rajput et al., 2011). Conversely, a decrease in SSTR2 was also observed in SZ postmortem brain samples by Beneyto et al. (2012).

Based on the increase in SSTR2 expression and NMDAR activity in HD as well as their simultaneous decrease in SZ, a direct correlation can be inferred. This may imply that SST+ interneurons are indeed associated with the hypofunction of NMDARs and hence the alterations of GBO in SZ. However, this relationship needs to be further investigated in this review and in future studies.

2. Methodology

2.1. Research design

This article reviews the evidence relating to SST+ GABAergic interneurons effects on cortical network oscillations and the cognitive deficits in SZ using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) system (Moher et al., 2015).

2.2. Literature search strategy

The search keywords (*schizophrenia*), (*NMDA**), (*Somatostatin or interneuron**), (*receptor**), and (*Oscillation* or wave* or rhythm*) were implemented in the Web of Science, Medline (PubMed), and Google Scholar to find the relevant resources through October 2016 to April 2016. Citations from review articles and significant papers were scrutinized to find additional related articles.

2.3. Inclusion criteria

The most relevant studies were included as their relevance was calculated based on whether they covered the following topics: NMDAR hypofunction, GABAergic interneurons, specifically those expressing SST, SSTRs, and changes in brain oscillations. Only original papers published in English were considered.

2.4. Quality assessment

The methodological quality of the studies included was evaluated based on the gold standard publication checklist (GSPC) for animal studies by Hooijmans et al. (2010) and the Cochrane Collaboration's tool for evaluating the risk of bias for the remaining studies (Higgins and Green, 2011). Critical appraisal of each study was conducted by means of systematic assessment of risks of bias, the relevance of populations, interventions and outcomes (Appendix A). Table 1 summarizes the studies reviewed in this research.

3. Results and discussions

3.1. Somatostatin changes in schizophrenia models

SST was analyzed by Hashimoto et al. (2008a) based on 14 pairs of SZ and control subjects with an extended cohort of 23 pairs for further investigations. DNA microarray analysis showed a 1.59 fold reduction in SST mRNA levels in SZ subjects when compared to control subjects. The results were verified by quantitative polymerase chain reaction (PCR) results showing a mean reduction of 44% in SST mRNAs in the DLPFC of schizophrenic subjects compared to control subjects ($p < 0.01$). The differences in mRNA expression detected by the quantitative PCR and the microarray analyses for SST were in fact highly correlated yielding a Pearson's correlation coefficient (r) of 0.79 ($p = 0.001$).

Assessment of SZ subjects through in situ hybridization, further verified the decrease in SST mRNA expression by 36% ($p = 0.001$) in the gray matter of SZ subjects. This correlated with the quantitative PCR results with $r = 0.90$ ($p < 0.001$). Indeed, SST expression exhibited the largest and most robust decrease of mRNA expressions found throughout the study.

Other areas of the neocortex such as the anterior cingulate cortex, the primary motor cortex and the primary visual cortex along with the DLPFC were investigated in a different study by Hashimoto et al. (2008b) 12 pairs of SZ and normal comparison subjects were included. The results indicated a mean decrease of 57% in SST transcript