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Treatment of the Prodrome of Schizophrenia

Introduction

The illness of schizophrenia (SCZ) has been crowded by mystery in defining and diagnosing the condition. It has been considered a unique disease for over a century, and while the boundaries and definitions have become more refined, its etiology and pathophysiology remain up to debate (R. Tandon et al., 2013). The widespread perception that schizophrenia tends to have a poor outcome is supported by research, which has found that many patients experience a chronic course leading to permanent disability (Walker et al., 2013). Because there is little evidence for reversal of the illness, it is crucial to consider preventative treatments during the onset of the disorder. The prodromal period is characterized by the period just preceding the onset of psychosis. Typically, SCZ treatments are directed at chronic symptoms, with a variety of antidepressants, anit-psychotics, and anxiolytics involved as the disease progresses. Preliminary findings suggested that antidepressants, either alone or in combination with other mood stabilizers and anxiolytics may be as effective in treating early stage prodromal symptoms as the novel antipsychotics that are currently on the market (B. Cornblatt et al., 2002). However, with an increasing depth in understanding, it has been shown that the excitatory/inhibitory (E/I)imbalances within the frontal cortex pose the promise for treating prodromal SCZ symptoms. Specifically, PV-interneurons that regulate GABA-ergic functions have been studied in relation to the pathophysiology of SCZ, showing areas for modulation in the GABA synapses to serve as regulation of E/I imbalances.

The Schizophrenia Prodrome

Accurate identifications of young people at risk for developing SCZ is critical for developing effective prevention programs and has implications for novel pharmaceutical treatments. The current DSM-5 diagnosis includes symptoms that are severe in nature. In order for a person to have SCZ, they must present with two or more of the following symptoms for a significant portion of time during a

1-month period. At least one of these should include: (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, (5) negative symptoms such as diminished emotional expression or avolition (Tandon et al., 2013). These are indispensable diagnostic criteria, however because these are extreme in their psychological nature, treatments for the prodromal phase are relevant for prevention of the disease. Venger et al. reviewed 137 patients with newly diagnosed psychosis. According to the analysis using the PANSS assessment, the absence of signs of an anxious state, conceptual disorganization of thinking, and emotional withdrawal are reliable signs of the prodromal period of psychosis in paranoid SCZ (Venger et al. 2024). Additionally, Cornblatt et al. Tested a modified strategy to improve prediction by selecting a more homogenous high-risk sample (attenuated positive symptom criteria only with an age range of mid-teens to early 20s) than is currently standard. In the study, a sample of 101 treatment-seeking adolescents (mean age, 15.9) at clinical high-risk for psychosis was followed clinically for up to 5 years. The overall conversion rate to psychosis was 28.3%. The final predictor model was able to predict with a validity of 81.8% and consisted of four variables: disorganized communication, suspiciousness, verbal memory deficits, and decline in social functioning during follow-up. These results supported the proposal that abnormalities other than attenuated positive symptoms have the potential to predict future psychosis (Cornblatt et al. 2015). Notably a focus on the cognitive deficits and negative symptoms (i.e. social withdrawal) were seen in those individuals with a high-risk of developing psychosis. Research into these physiology and related biomarkers related to symptoms of cognitive decline and negative for individuals with SCZ has become a growing body of interest.

Pathophysiology of SCZ

Genetic liability has been identified for SCZ, however individuals exert a minute influence on the overall risk for development of the disease. Preexisting susceptibility and environmental factors are thought to interact during critical periods of vulnerability, such as during childhood and adolescence. Stress during these periods have been linked to SCZ due to its deleterious effects upon inhibitory circuit

maturation (Uliana et al., 2024). These alterations are particularly present in individuals with changes in behavior, cognition, and mood. A history of genetic vulnerability or stress can be considered at a high-risk stage preceding full-blown SCZ symptoms. Notably these alterations are observed in first-episode psychosis and may even predict the transition from clinical high-risk states. Uliana et al. reported that exposing rats to a combination of stressors during adolescence leads to ventral hippocampal hyperactivity and alters PV interneuron function. This is thought to be because components of the extracellular matrix and the perineuronal nets (PNNs) serve a protective function for PV interneurons are still under development during this time, leaving PV interneurons more susceptible to stressors, such as oxidative stress and excitotoxicity. PNNs act as buffering mechanisms for fast-spiking PV interneurons (Uliana et al., 2024). In turn, GABAergic and glutamatergic imbalance in the hippocampal circuit dysfunctions could lead to positive, negative, and cognitive symptoms. Consequently, establishing an E/I balance could lead to novel strategies in addressing the diverse symptoms of SCZ, especially the negative and cognitive symptoms seen in the prodromal phase. Addressing the GABAergic and glutamatergic function could theoretically be done through drive increasing the postsynaptic actions of GABA or by increasing in PV interneuron drive (Uliana et al., 2024). The aim with all of these methods is to address the E/I imbalance that is seen in patients with SCZ.

Parvalbumin (PV)-containing GABAergic interneurons

PV interneurons are characterized electrophysiologically by their fast-spiking activity, which allows them to exert significant control over the excitability of pyramidal neurons. This feature highlights the role of PV interneurons as pivotal regulators of the E/I balance, despite only constituting a fraction of the overall GABAergic interneurons in combination with somatostatin and vasoactive intestinal peptide expressing interneurons. PV interneuron-mediated inhibition may shift the E/I ratio, resulting in disruptions in brain circuitry and ultimately resulting in high-order behavioral symptoms. Oscillatory activity, specifically gamma oscillations (30-80 Hz), play an important role in the coordinated functions

of neural networks. This range of oscillations are crucial for cognitive processes and rely on the functioning of PV interneurons (Uliana et al., 2024).

Excitation/Inhibition Imbalances

Current pharmacotherapy for the disease predominantly focuses on one mechanism, the dopamine D2 receptor blockade. However, the dopamine D2 receptor blockade often shows limited efficacy and poor tolerability. Howes et al. reviewed the latest meta-analyses and other findings on the neurobiology of prodromal, first-episode and chronic schizophrenia and their link to psychotic symptoms. The main focus of studies has been in the striatum where more than 50 molecular imaging studies showed evidence of alterations. Additionally, the researchers illuminated glutamatergic impairment in SCZ. Glutamate is the main excitatory neurotransmitter in the brain and acts on ionotropic and metabotropic glutamate receptors. The ionotropic glutamate receptors include α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kianate and N-methyl D-aspartate (NMDA) subtypes. Metabotropic receptors are subdivided into three groups and mainly regulate presynaptic and postsynaptic actions. It was identified that mRNA and protein levels of the GluN1 subunit of the NMDA receptor are significantly lower in the prefrontal cortex of people with SCZ. The evidence demonstrated that neurotransmitter alterations occur in regionally specific areas of the brain. These included higher glutamate and dopamine measures in the basal ganglia, and lower glutamate, dopamine, and γ-Aminobutanoic acid (GABA) levels in cortical regions, specifically the frontal cortex, relative to healthy individuals (Howes et al. 2024). Treatment of the prodrome focuses on these brain areas as regions of interest for neurotransmission alterations.

There were also GABAergic perturbations in SCZ and GABA alterations in people with SCZ. GABA is the most common inhibitory neurotransmitter in the human brain. Post-mortem studies of people with SCZ compared with those who don't have the disorder have mostly focused on the frontal cortex. There were lower markers of mRNA for numerous levels of GABA markers such as the enzyme glutamic acid decarboxylase 67 (GAD67). Additionally there was evidence for lower activity of

parvalbumin-positive GABAergic interneurons, which have a key role in coordinating fast firing of glutamatergic neurons. In the past decade, the imaging findings have been merged into an integrated model to consider how the glutamatergic, GABAergic and dopaminergic systems might interact to explain the imaging findings and symptoms of the disorder. The altered E/I signaling in frontal cortical regions and altered excitatory signaling in the basal ganglia and thalamus in SCZ, although the cause of these alterations remains to be clarified. The findings indicate that glutamate and dopamine alterations in the basal ganglia are linked to greater severity of symptoms. (Howes et al. 2024).

E/I imbalance in SCZ

Uliana et al. reported that E/I balance dysfunction in SCZ is evidence in several ways. In humans, decreased levels of GABA were identified in cerebrospinal fluid levels in individuals with SCZ. GABA is a wide reaching neuron therefore GABA decrease is observed in different brain areas related to SCZ pathophysiology, including the dorsolateral prefrontal cortex, anterior cingulate cortex, and hippocampus, among others. In vivo evidence suggested that GABA levels were associated with symptom severity in first-episode psychosis. Postmortem studies have revealed structural and functional alterations in inhibitory GABAergic circuits. A functional loss of PV interneurons in the hippocampus and prefrontal cortex in individuals with SCZ. One particular component of the GABAergic system that is essential for generating and maintaining the E/I balance is the parvalbumin (PV)-containing GABAergic interneuron, which develops extensively during adolescence (Uliana et al., 2024).

Increasing Post Synaptic actions of GABA

Multiple studies have suggested that augmenting GABAergic signaling via PV interneuron modulation can be effective in ameliorating deficits in working memory, cognitive flexibility and sociability in animal models of psychiatric disease. There is a large breadth of scientific literature that suggests GABAergic hypofunction in the human PFC represents a final common pathway in the cognitive symptoms in SCZ. GABA agonists have reached Phase II clinical trials for the treatment of social

disability in ASD, but so far have only focused on α2/α3-GABAARs (Ferguson et al., 2024). Positive effects in GlyT1 receptors for neuroplasticity have been reported which support further investigation of GlyT1 inhibitors in the treatment of SCZ symptoms. Additionally, Iclepertin is a novel potent and selective GLyT1 inhibitor, currently under development. Currently, the safety, pharmacokinetic profile, and efficacy of Iclepertin has been investigated in several Phase I and II clinical trials but still requires more research (Rosenbrok et al., 2023).

Impairment of PV interneurons

In SCZ, the functional impairment of PV interneurons might stem from either a loss of PV interneurons in the hippocampus or a reduction in PV interneuron activity in the hippocampus and prefrontal cortex, possibly due to dysfunction of glutamate NMDA receptor drive (Uliana et al., 2024). Evidence from studies that modulate via other pathways also supports targeting glutamatergic signaling to improve cognition. D-serine and D-aspartate and D-amino acids play key roles in the pathogenesis of SCZ. Sodium benzoate, a D-amino acid oxidase inhibitor, when administered at a dose of 2 g per day as an adjunct to clozapine treatment, improved positive and negative symptoms as well as quality of life measures in patients with a placebo (Rosenbrock et al., 2023). Another D-amino acid oxidase inhibitor, luvadaxistat is currently being investigated as a potential treatment. Given the evidence for the role of NMDA hypofunction in SCZ symptoms, it's theorized that increasing synaptic glycine levels by GlyT1 inhibition could normalize NMDA receptor function. Thus this action could facilitate glutamatergic signaling and synaptic plasticity. This would normalize NMDA receptor-mediated E/I imbalances in the cortex. Ultimately these actions should lead to cognition improvements in patients (Rosenbrock et al., 2023). Therefore, inhibitors of GlyT1, which block the reuptake of glycine, could offer a promising treatment approach.

Discussion

Considering that abnormalities in the stress response early in life predispose individuals to SCZ, its early identification would allow interventions to decrease the stress impact as a means of prevention. By targeting PV interneurons, treatments are able to address specific pathways in the Glutamate/GABA excitation model that can contribute to the onset of SCZ. Individuals with a genetic predisposition to the illness and who are exposed to certain environmental stressors are at the most risk for developing the disorder. Understanding what the behavioral signs and the behavioral neuroscience behind these symptoms are is important for creating successful transitions into the more severe symptoms of psychosis. Additionally, understanding the facts of SCZ is important for reducing its stigma. This is especially important for families, who can provide the most help for someone facing psychiatric illness. Increasing education and acceptance can help reduce stigma surrounding the SCZ prodrome and encourage members to seek treatments and early therapies. Knowing how genetics and environmental factors play into this debilitating disease, early therapies are of the utmost efficacy in reducing its progression. Furthermore, the E/I imbalance has been an avenue for expansive research into the mechanisms that underlie the prodrome of SCZ. e E/I balance is the parvalbumin (PV)-containing GABAergic interneuron, which develops extensively during adolescence (Uliana et al., 2024). PV-interneuron, which develops extensively during adolescence (Uliana et al., 2024). In particular, a component of the GABAergic system that is essential for generating and maintaining the E/I balance is the parvalbumin (PV)-containing GABAergic interneuron, which develops extensively during adolescence. Targeted modulation of the PV could theoretically be done through increasing the postsynaptic actions of GABA or increasing in PV interneuron. However, evidence is currently limited in their effectiveness. Additionally, many PV modulations that are not mentioned in this paper come with side effects and more research is required to understand what long term treatments will be beneficial. All this considered, E/I imbalances are signatures to many mood/psychiatric disorders and research into the PV-interneuron goes beyond the scope of SCZ. Other mechanisms of investigation such as metabolomics and neurodynamics could be employed to create a wider picture for therapy. Ultimately, if successful manipulations of PV interneurons

can be linked to physiological signatures that can be observed using less invasive recording approaches such as oscillatory patterns, we can potentially determine biomarkers for behavior therapies in humans for individuals with SCZ (Ferguson et al, 2024).

Conclusion

Overall, SCZ is a complex disease that has been hard to untangle due to its multifactorial mechanistic pathways that we do not fully understand yet. Its pathophysiology is unique in that while genetic risk occurs, environmental factors during the adolescent stages of life significantly shape whether or not someone will develop SCZ. Research into the physiological signatures of the prodromal stage of the SCZ is important for developing therapies that target the correct pathways. Most notably, a shift of research focus towards the hypodopaminergic pathways and E/I imbalance is essential in diagnosing and treating the prodromal signatures of SCZ. Augmenting release of GABA via the PV interneurons and additional GABA/Glutamate signaling neurons provide avenues for future research in unpacking this important paradigm.

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