Snapshot of Schizophrenia: Current Knowledge and Prospects

Ruixue Gao1,*

1School of Life Sciences Sciences, Tsinghua University, Beijing, China

Abstract. Schizophrenia is a widely known mental disorder that can cause severe life struggles if not being treated properly. According to its diagnose, patients suffer from delusions, hallucinations, and other disorders. For treatment, antipsychotics are commonly used, but their efficiency cannot be promised due to the lack of knowledge about this illness. In previous studies, scientists had suggested neuronal, genetic, epigenetic, and immunological factors. However, to fully understand the mechanism of schizophrenia, there is still a long way to go for understanding how these factors interact and induce dysfunction.

1 Introduction

Schizophrenia is a severe mental disorder that was first defined in 1911 by Paul Eugen Bleuler to regard the split of different cognitive functions [1]. Recent statistics show that nearly 20 million people have schizophrenia globally in total [2]. The onset of schizophrenia often occurs when patients are between 16 to 30 years old and affects patients throughout their lives. The diagnosis and treatment of schizophrenia are complicated as similar symptoms can have various causes. Both genetic information and environmental factors can cause schizophrenia. Relatives with schizophrenia indicate a high rate of suffering from the same disorder, while drug use and pressure are environmental factors that can cause schizophrenia [3].

Many people misunderstand the concept of schizophrenia to indicate a mental disorder having multiple personalities, although it suggests disrupted mental processes. Typically, positive symptoms of schizophrenia include delusion, hallucination, disorganized speech, and disorganized behaviour, while schizophrenia also displays negative symptoms, such as loss of motivation [4]. The symptoms of a schizophrenia patient change over time and might have different severity. Roughly 10% of schizophrenia patients will die because of suicide, while up to 50% percent of individuals with schizophrenia might have suicide attempts. On average, the onset of schizophrenia causes a 10-year reduction in lifespan [5]. For schizophrenia patients, the thought of committing suicide can lead to actual attempts in a short period. Thus, treatment in time is very important for them.

As schizophrenia might have different causes, its treatments can also vary. Typically, patients are prescribed different antipsychotic drugs. Treatment for schizophrenia is crucial, even though it remains incurable. About half of these patients can benefit from traditional antipsychotic therapy and reduce their positive symptoms. However, there are still many limitations in the current treatment. Side effects commonly appear, and a high relapse rate might nullify previous efforts. As reported, over 50% of schizophrenia patients suffer from chronic symptoms even after the treatment [6]. Thus, scientists are developing new drugs for alternative targets in the treatment [7]. Factors both inside and outside of the nervous system have been identified. Moreover, a more comprehensive understanding of schizophrenia has been reached currently. Defects in other systems besides the nervous system have been identified, leading to the discovery of novel therapeutic methods.

2 Diagnosis and therapy

For studying schizophrenia, knowing the definition of this disease is essential. Nowadays, the diagnosis of schizophrenia is primarily according to the Eleventh Revision of the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual, Fifth Edition (DSM-V) [4, 8]. As stated in DSM-V, the primary concern of accurate diagnosis is the duration of symptoms. Patients should present at least two symptoms: delusion, hallucination, disorganized speech, grossly disorganized, and negative symptoms for at least 1 month. Furthermore, they should display dysfunctions on major life issues, for example, work or relations. This dysfunction should last for 6 months, including the 1 month of symptoms and following residual periods [4].

Compared with other psychological disorders, schizophrenia is distinguished from schizoaffective disorder and other dysthymic disorders by a minority of manic and mood episodes. Diagnosis should be especially aware of the patient’s history of autism spectrum disorder and communication disorder, as they might attribute to similar symptoms of schizophrenia. Thus, patients with an early onset of these two kinds of disorders are only diagnosed if they experienced persistent delusions or hallucinations. Finally,
dysfunctions that occur under special physiological conditions are ruled out to ensure that these symptoms are due to mental dysfunction [4].

After diagnosed, antipsychotic drugs are commonly applied to treat schizophrenia. They are antagonists of dopamine receptors and are supposed to alleviate the positive symptoms of schizophrenia through this pathway. However, many of these antagonists’ affinity is not restricted to dopamine receptors. They are likely to interact with other neurotransmitter receptors, especially serotonin receptors, and might cause unfavorable side effects. Moreover, these drugs are less effective in treating negative symptoms of schizophrenia. About 30% of schizophrenia patients are resistant to drug treatment, probably due to the polymorphism of receptors [9].

According to the timeline, there are three generations of antipsychotic drugs. The first-generation antipsychotics date back to 1950 and function mainly through blocking dopamine D2 receptors of the whole brain uniformly [10]. The second-generation drugs are aimed to reduce side effects while establishing a more substantial effect on negative symptoms through their stronger inhibition of serotonin 5-HT2A receptors and milder antagonism on D2 receptors [11]. Finally, the third-generation antipsychotics work through partial blockage of D2 receptors at high dopamine concentration [9]. The evolution of antipsychotic drugs has made significant progress. However, further improvement of schizophrenia treatment is still limited by the knowledge of its causation [9]. Thus, to provide better treatment, a more comprehensive understanding of schizophrenia-related factors is needed.

3 Factors that induce schizophrenia

3.1. Neuronal factors

As long as schizophrenia was defined, its patients’ deflection in various executive functions was hypothesized to be linked to brain abnormality. With the development of tools in studying neuropsychological deficits, scientists started to identify numerous abnormal structures in schizophrenia patients’ brains. Now, schizophrenia is regarded as a neurodevelopmental disorder rather than just impairment of brain function, which suggests that neurological abnormalities play the central role in schizophrenia onsets. Specifically, scientists have proposed a two-step model of the abnormalities in schizophrenia neurodevelopment, including pre-perinatal defects, which are later enlarged during adolescence development [12].

To detect both the structural and functional deficits in schizophrenia brains, scientists have applied different tools, including computed tomography (CT), magnetic resonance imaging (MRI), event-related potentials (ERPs), and functional MRI (fMRI). Enlarged ventricles combined with defects in cortical and subcortical regions were identified as structural deficiencies [12]. As the structure is the foundation of function, these abnormalities in brain regions induced its dysfunction. The loss of grey matter in the frontal lobe correlates with executive capacity loss [13]. Through ERPs, scientists have found that P300, a late positive potential linked to the reflection of the stimulus’s content, is reduced in schizophrenia patients [14]. Moreover, their gamma-band evoked by auditory stimulus was also defective [15]. Scientists have also observed schizophrenia patients’ brain activity while doing tasks. They found out that the prefrontal cortex and parietal cortex activity had established altered patterns when doing working memory tasks [16].

As the fundamental component of the nervous system, synapses also show dysfunction in the nervous system of schizophrenia patients. As various antipsychotics, which are dopamine receptor antagonists, are proved to be effective in schizophrenia treatment, scientists established the dopamine hypothesis to describe the synaptic dysfunction in schizophrenia [16]. Davis and his colleagues suggested that dopamine receptors’ activation is differentially influenced in this syndrome, with reduced activity in the frontal area and increased activity in striatum corpora [17]. Now, most scientists agree that abnormal dopamine secretion attributes to aberrant salience [18]. Besides dopamine, glutamate is another neurotransmitter that might attribute to schizophrenia. According to the impairment of cognitive functions in schizophrenia, rescuing glutamatergic synapses might help reduce the symptoms. As glutamatergic neurons’ activity can affect synaptic plasticity, its dysfunction might be linked to brain structure abnormalities [10].

However, schizophrenia’s abnormality is not limited to the nervous system. Schizophrenia patients also show defects in many other aspects. From the view of hereditary, the onset of schizophrenia might correlate with mutations in genes. Special gene modification might induce expression abnormalities. Moreover, the immune system in schizophrenia patients might also display defects, especially in its interaction with the nervous system.

3.2. Genetic factors

In the studies on genetic factors which induce schizophrenia, scientists had identified single nucleotide polymorphisms (SNPs) and copy number variants (CNVs). Currently, scientists are also applying the method of next generation sequencing to identify rare point mutations that cannot be identified in simple studies of SNPs and other small indels [19].

Through genome-wide association studies (GWAS), they had discovered 108 loci that increase the risk of schizophrenia if mutated. Among them are genes encoding protein targets in schizophrenia treatment and factors in glutamatergic neurotransmission. There are also genes encoding proteins in the calcium signal pathway and other synaptic functions [20]. Genes encoding immunological pathways were also identified, bringing out a new prospect of schizophrenia researches [21].
In the analysis of CNVs, researchers were focused on chromosomal rearrangements, influencing more than 1 kb in length. Even though these variants rarely occur, scientists still found many significant loci, including genes encoding N-methyl-D-aspartate receptor (NMDAR) and neuronal activity-regulated cytoskeleton-associated (ARC) postsynaptic signalling complexes [22].

By using next generation sequencing, scientists have identified SETD1A, a transcription regulator that catalyses methylation of histone H3 subunit, as a candidate for rare mutations that can cause schizophrenia [23].

Even though there are plenty of outcomes from genetic studies of schizophrenia, the limitation of these studies is also apparent. In the GWAS, which has identified most loci, less than 5% of disease variance can be explained [19]. A strict selection might have prevented many loci from being observed in a large-scale analysis and reduced the robustness between different studies [19]. Thus, there are still many unknown in schizophrenia genetics.

3.3. Epigenetic factors

Epigenetic factors that might influence the risk of schizophrenia include DNA methylation and histone modifications.

In one study, scientists had found that DNA methylation at the promoter region of an isoform of glutamic acid decarboxylase was significantly reduced in schizophrenia patients [24]. Similarly, increased repressive methylation at CpG island at RELN promoter might explain the reduction of RELN expression, which is crucial for neuronal development [25]. To establish a stronger linkage between epigenetic factors and schizophrenia, scientists found that a schizophrenia mouse model built by repeated L-methionine injection displays higher methylation at the RELN promoter [26].

Histone modifications might also influence the risk of schizophrenia onset, as antipsychotic drugs, which are dopamine D2 receptor antagonists, can induce its H3 subunits’ phospho-acetylation [27]. Among histone deacetylases (HDACs), HDCA2 was identified as a possible target for cognitive deficits treatment in schizophrenia [28]. Moreover, TSA, an HDCA inhibitor, was also found to reduce anxiety-like behaviors caused by maternal stress of infection [29].

3.4. Immune factors

Scientists have long discovered the correlation between prenatal infections and schizophrenia and have realized the significance of the immune system in its onset [30]. In one of the studies, scientists found that a kind of inflammatory protein, fibrin, increased in the cerebrospinal fluid (CSF) of 50% of schizophrenia patients [31]. Another research on cytokines, which regulates inflammation, also showed a significant increase of proinflammatory cytokines in schizophrenia patients’ CSF [32]. However, the robustness of this finding is restricted by the correspondence between immune factors and other high-risk factors, such as smoking and medication.

Furthermore, scientists have found direct influences of interleukins (ILs) on neuronal development. For example, IL-1β can induce dopaminergic synapses, and IL-6 can inhibit serotonergic neurons’ survival [33, 34]. Despite that there might be a general correlation between immune activity and psychiatric disorders, specialized immune abnormality contributes to schizophrenia was also identified. An increase in the number of dopaminergic neurons in the midbrain can be observed in fetal mice after an infection in their pregnant mother, and the same kind of neurons is supposed to involve in schizophrenia pathology [35]. Contradictory, an opposite effect of immune factor interferon-α was detected to reduce dopamine release in the striatum [36]. These contradictory findings reveal the complexity of the immune system’s influence on schizophrenia.

4 Conclusions

Till now, scientists have reached many achievements in studies of schizophrenia. However, due to its complexity, there is still much to know about it. Scientists have not yet identified the cause of schizophrenia. These currently exist hypotheses have covered various kinds of neurons, but they have not been integrated, and factors’ importance hierarchy has not been illustrated. Moreover, as many of these hypotheses are derived from antipsychotic treatments and compare studies of schizophrenia patients and control group, we still need further investigation to establish causation instead of correlation. Due to the development of new technologies, scientists have found factors other than neuronal defects, which might significantly impact schizophrenia onset. However, it is still unknown whether they occur before neuronal abnormalities or they display as outcomes.

There are still difficulties in studies of schizophrenia, as it can display a large variance of symptoms and severity. Due to ethical concerns, studies of schizophrenia largely depend on animal models, which might deviate from actual human patients. However, as people are more and more exposed to pressure and aware of mental disorders, the diagnosis and treatment of schizophrenia will need to be improved. It seems impractical to find a single cure for all schizophrenia patients. Thus, it might be more realistic to establish a classification of different schizophrenia subtypes that can correspond to accurate medical treatment.

References

1. D. Hell, C. Scharfetter, A. Möller, Eugen Bleuler, Leben und Werk. (2001)

2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, Lancet, 392, 1789-1858 (2018)

3. K.T. Mueser, S.R. McGurk, Lancet, 363, 2063–2072 (2004)
4. American Psychiatric Association, *Diagnostic and statistical manual of mental disorders, fifth edn* (2018)

5. L. Sher, R.S. Kahn, Medicina (Kaunas) 55, 361 (2019)

6. T.S. Stroup, J.A. Lieberman, M.S. Swartz, J.P. McEvoy, Dialogues Clin. Neurosci. 2, 373–379 (2000)

7. N.P. Maric, M.J. Jovicic, M. Mihaljevic, C. Miljevic, Drug Dev. Res. 77, 357–367 (2016)

8. World Health Organization, *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (2010)

9. P. Stepincki, M. Kondej, A.A. Kaczor, Molecules, 23, 2087 (2018)

10. F. López-Muñoz, C. Alamo, E. Cuenca, W.W. Shen, P. Clervoy, G. Rubio, Ann Clin Psychiatry, 17, 113–135 (2005)

11. P.G. Strange, Pharmacol. Rev. 53, 119–133 (2001)

12. L.J. Seidman, A.F. Mirsky, J Int Neuropsychol Soc, 23, 881–892 (2017)

13. North American Prodrome Longitudinal Study Consortium, Biol. Psychiatry, 77, 147-157 (2015)

14. C.C. Duncan, W.M. Perlstein, J.M. Morhisa, Electroencephalogr Clin Neurophysiol Suppl. 40, 670–674 (1987)

15. G. Leicht, S. Karch, E. Karamatskos, I. Giegling, H.J. Möller, U. Hegerl, O. Pogarell, D. Rujescu, C. Mulert, J Psychiatr Res, 108, 699–705 (2011)

16. D.C. Glahn, J.D. Ragland, A. Abramoff, J. Barrett, A.R. Laird, C.E. Bearden, D.I. Velligan, Hum. Brain Mapp. 25, 60–69 (2005)

17. K. L. Davis, R.S. Kahn, G. Ko, M. Davidson, Am. J. Psychiatry, 148, 1474–1486 (1991)

18. S. Kapur, Am. J. Psychiatry, 160, 13–23 (2003)

19. C. Foley, A. Corvin, S. Nakagome, Curr Psychiatry Rep, 19, 61 (2017)

20. Schizophrenia Working Group of the Psychiatric Genomics Consortium, Nature, 511, 421-427 (2014)

21. Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, Nat. Neurosci. 18, 199–209 (2015)

22. G. Kirov, A.J. Pocklington, P. Holmans, D. Ivanov, M. Ikeda, D. Ruderfer, J. Moran, K. Chambert, D. Tonecheva, L. Georgieva, D. Grozeva, M. Fjodorova, R. Willeront, E. Rees, I. Nikolov, L.N. van de Lagemaat, A. Bayès, E. Fernandez, P.I. Olason, Y. Böttcher, N.H. Komiyama, M.O. Collins, J. Choudhary, K. Stefansson, H. Stefansson, S.G. Grant, S. Purcell, P. Sklar, M.C. O'Donovan, M.J. Owen, Mol. Psychiatry, 17, 142–153 (2012)

23. T. Singh, M.I. Kurki, D. Curtis, S.M. Purcell, L. Crooks, J. McRae, J. Suvisaari, H. Chheda, D. Blackwood, G. Breen, O. Pietiläinen, S.S. Gerety, M. Ayub, M. Blyth, T. Cole, D. Collier, E.L. Coomber, N. Craddock, M.J. Daly, J. Danesh, M. DiForti, A. Foster, N.B. Freimer, D. Geschwind, M. Johnstone, S. Joss, G. Kirov, J. Körkkö, O. Kuismin, P. Holmans, C.M. Hultman, C. Iyegbe, J. Lönqvist, M. Männikkö, S.A. McCarroll, P. McGuffin, A.M. McIntosh, A. McQuillin, J.S. Moilanen, C. Moore, R.M. Murray, R. Newbury-Ecob, W. Ouwehand, T. Paunio, E. Prigmore, E. Rees, D. Roberts, J. Sambrook, P. Sklar, D. St Clair, J. Veijola, J.T. Walters, H. Williams; Swedish Schizophrenia Study; INTERVAL Study; DDD Study; UK10 K Consortium, P.F. Sullivan, M.E. Hurles, M.C. O'Donovan, A. Palotie, M.J. Owen, J.C. Barrett, Nat. Neurosci. 19, 571–577 (2016)

24. H.S. Huang, S. Akbarian, PLoS One, 2, e809 (2007)

25. H.M. Abdolmaleky, K.H. Cheng, A. Russo, C.L. Smith, S.V. Faraone, M. Wilcox, R. Shafa, S.J. Glatt, G. Nguyen, J.F. Ponte, S. Thiagalingam, M.T. Tsuang, Am. J. Med. Genet. B 134, 60–66 (2005)

26. E. Dong, A. Guidotti, D.R. Grayson, E. Costa, Proc. Natl. Acad. Sci. U.S.A. 104, 4676–4681 (2007)

27. J. Li, Y. Guo, F.A. Schroeder, R.M. Youngs, T.W. Schmidt, C. Ferris, C. Konradi, S. Akbarian, J. Neurochem. 90, 1117–1131 (2004)

28. J.S. Guan, S.J. Haggarty, E. Giacometti, J.H. Dannenberg, N. Joseph, J. Gao, T.J. Nieland, Y. Zhou, X. Wang, R. Mazitschek, J.E. Bradner, R.A. DePinho, R. Jaenisch, L.H. Tsai, Nature, 459, 55–60 (2009)

29. I.C. Weaver, M.J. Meaney, M. Szyf, Proc. Natl. Acad. Sci. U.S.A. 103, 3480–3485 (2006)

30. H.J. Sørensen, E.L. Mortensen, J.M. Reinisch, S.A. Mednick, Schizophr Bull, 35, 631–637 (2009)

31. D.B. Wildenauer, D. Korschenhausen, W. Hoechtl, M. Ackenhil, M. Kehl, F. Lottspeich, Electrophoresis, 12, 487–492 (1991)

32. A.K. Wang, B.J. Miller, Schizophr Bull, 44, 75–83 (2018)

33. A. Kabiersch, H. Furukawa, A. del Rey, H.O. Besedovsky, Ann. N. Y. Acad. Sci. 840, 123–127 (1998)

34. L.F. Jarskog, H. Xiao, M.B. Wilkie, J.M. Lauder, J.H. Gilmore, Int. J. Dev. Neurosci. 15, 711–716 (1997)

35. C. Winter, A. Djordje-Isnani, R. Sohr, R. Morgenstern, J. Felden, G. Juckel, U. Meyer, Int. J. Neuropsychopharmacol. 12, 513–524 (2009)

36. J.C. Felger, J. Mun, H.L. Kimmel, J.A. Nye, D.F. Drake, C.R. Hernandez, A.A. Freeman, D.B. Rye, M.M. Goodman, L.L. Howell, A.H. Miller, Neuropsychopharmacology, 38, 2179–2187 (2013)