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Review

Epigenetic signaling in schizophrenia

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ABSTRACT

Histone modifications and DNA methylation represent central dynamic and reversible processes that regulate gene expression and contribute to cellular phenotypes. These epigenetic marks have been shown to play fundamental roles in a diverse set of signaling and behavioral outcomes. Psychiatric disorders such as schizophrenia and depression are complex and heterogeneous diseases with multiple and independent factors that may contribute to their pathophysiology, making challenging to find a link between specific elements and the underlying mechanisms responsible for the disorder and its treatment. Growing evidences suggest that epigenetic modifications in certain brain regions and neural circuits represent a key mechanism through which environmental factors interact with individual's genetic constitution to affect risk of psychiatric conditions throughout life. This review focuses on recent advances that directly implicate epigenetic modifications in schizophrenia and antipsychotic drug action.

Contents

1. Introduction

Schizophrenia is a chronic, debilitating mental disorder that affects about 1% of the world's population [1–5]. It is estimated to be the seventh most costly medical illness to society in terms of cost of care and loss of productivity, with rates of prevalence that are similar throughout diverse cultures and geographic areas. Diagnostic features of schizophrenia include hallucinations and delusions. In addition to these psychotic or "positive" symptoms, various deficits or negative symptoms occur, including inability to pay attention, the loss of sense of pleasure, and social withdrawal. Cognitive deficits, such as abnormalities in memory, perception, motor functioning, and language processing, are also

Abbreviations: ARC, activity-regulated cytoskeleton-associated scaffold protein; AVP, arginine vasopressin; ChIP, chromatin immunoprecipitation; DISC1, disrupted in schizophrenia 1; FSL, flinders sensitive line rats; GABA, γ-aminobutyric acid; GAD67, 67 kDa isoform of glutamic acid decarboxylase; GDNF, glial cell-derived neurotrophic factor; GR, glucocorticoid receptor; GWAS, genome-wide association study; HAT, histone acetyl transferases; HDAC, histone deacetylases; LY341495, mGlu2/3 receptor antagonist; LY354740, mGlu2/3 receptor agonist; LY379268, mGlu2/3 receptor agonist; MK801 (dizocilpine), non-competitive NMDA receptor antagonist; NMDA, N-methyl-D-aspartate; PV, parvalbumin; TSA, trichostatin A (HDAC inhibitor).

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essential features in schizophrenia that substantially account for limitations in functional outcomes associated with this disease such as work, independent living and social relationships [6–9].

The available symptomatic treatment is only partially successful, and therefore the development of rational therapeutics, based on an understanding of the etiology and pathogenesis of schizophrenia, is imperative [10–14]. Advances in the understanding of schizophrenia have been limited by a number of factors, including the heterogeneity in its phenotype, and the lack of clear pathological lesions like those that have provided reference points in the study of neurological diseases such as Alzheimer's and Parkinson's. Both typical, such as chlorpromazine and haloperidol, and atypical, such as clozapine and olanzapine, were serendipitously discovered as secondary effects of drugs tested for different therapeutic targets. For instance, the first antipsychotic drug chlorpromazine was discovered in 1952 as an antihistaminic which appeared to actually decrease psychosis [15]. Haloperidol was designed as a pain reliever [16], and clozapine was described in 1958 as "tricyclic antidepressant but with *neuroleptic* properties" [17,18]. Following these early discoveries, both the mechanisms of actions of antipsychotic drugs and the molecular basis of schizophrenia have been the focus of much attention in basic and translational neuroscience research. As yet, the pharmacological profiles of all the antipsychotic medications currently prescribed have in common a high affinity for monoaminergic neurotransmitter receptors, including dopamine D_2, dopamine D_1, serotonin 5-HT_{2A}, serotonin 5-HT_{2C}, serotonin 5-HT_{1A}, adrenergic $\alpha_{1A/1B}$, adrenergic $\alpha_{2A/2B/2C}$, and muscarinic $M_{1/2/3/4/5}$ [19]. Furthermore, whereas in some patients with schizophrenia both typical and atypical antipsychotic drugs produce either complete or partial remission of "positive" psychotic symptoms, these medications currently available are ineffective against cognitive deficits, and consequently treated patients have either small improvements or even deterioration in several cognitive domains [20–24]. During recent years, as it has become clearer that epigenetic molecular mechanisms, specifically DNA methylation and chromatin modification, generate and maintain behavioral changes in animal models, functional and translational approaches are more needed to characterize the basic signaling and neuronal circuit processes whereby drugs that directly or indirectly affect nucleosome structure and function, and its implications in CNS function [25–32]. Here we review recent observations that implicate epigenetic signaling mechanisms as a novel target to treat schizophrenia and other psychiatric disorders.

2. Schizophrenia: genes and environment

Schizophrenia has traditionally been viewed as a genetic disorder with heritable rates estimated at 73–90%. This hypothesis was strengthened by genome-wide search studies in the mid-2000s that showed schizophrenia-associated genetic alterations including large recurrent microdeletions [33], copy number variations [34], and rare chromosomal microdeletions and duplications [35] especially in neurodevelopmental pathways [36]. Results of these studies also suggest that the risk of schizophrenia is associated with polygenic pathways involving thousands of common alleles each of which with a very small effect [37]. More recent large genome-wide association study (GWAS) arrays have narrowed down the list of genetic loci associated with schizophrenia. Notably, several of these genes include dopamine D_2 (*DRD2*) and serotonin 5-HT_{2A} (*Htr2a*) receptors, as well as genes involved in glutamatergic neurotransmission [38], voltage-gated ion channel, and the signaling complex formed by activity-regulated cytoskeleton-associated scaffold protein (ARC) at the postsynaptic density [39]. These findings might allow the classification of subjects with schizophrenia on the basis the pathways involved in their etiology.

Nevertheless, although as discussed above, alterations in the genetic code are assumed to play a fundamental role in schizophrenia-risk, these are not the only factors responsible for the disease. As an example, monozygotic twins, who share almost 100% of their genetic material, have a 50% concordance rate for schizophrenia relative to the 15% concordance for dizygotic twins [40–42]. Such results further support a significant contribution of genetic factors to this complex disease. At the same time, however, they also attribute an important role of environmental factors in the development of schizophrenia-related neuropsychological deficits. Epidemiological studies have indicated that maternal exposure during pregnancy to infectious agents, including virus (influenza [43–45] and rubella [46]), bacteria (bronchopneumonia) [47], and protozoa (*Toxoplasma gondii*) [48] significantly increase the risk of schizophrenia in the adult offspring. As an example, the Spanish influenza pandemic of 1918–1919, whose coding sequence has recently been used to characterize the extraordinary virulence of the reconstructed 1918 influenza pandemic virus [49], was contracted by more than 500 million individuals worldwide. In 1919, Karl Menninger published a classic article describing for the first time an association of influenza and psychoses in patients [44]. These findings have been validated in numerous population groups, and more recent nested case–control studies showed that the risk of schizophrenia is increased 7-fold for maternal influenza infection during the first trimester of pregnancy [43].

Additionally, maternal adverse life events that occurred during pregnancy, such as war [50,51], famine [52], and death or illness in a first-degree relative [53], have been associated with an elevated risk of schizophrenia in the adult offspring. Based on these epidemiological studies, numerous research groups have developed rodent models of influenza viral infection [54–60] and maternal variable and severe variable and unpredictable stress [61–64] that induce schizophrenia-related biochemical and behavioral changes in the newborns. Remarkably, these animal models of prenatal insults during pregnancy support a uniform conclusion that changes in the adult offspring are related to alterations in the maternal immune system, with immune components particularly influential such as TNF-α, IL-1β, IL-6 and IL-8 [65–70]. Interesting is also the finding that the incidence of schizophrenia is strongly increased in people born and raised in cities as compared to rural areas [71]. Additional basic experimental and clinical studies are needed to interrogate the molecular mechanisms whereby genes and environment interact to influence schizophrenia risk.

3. Basic concepts in epigenetics

The first sequencing and analysis of the human genome in 2001 are considered as a fundamental landmark in biological research [72,73]. However, all the diploid somatic cells in eukaryotic multicellular organisms share a virtually identical genome, whereas their function is completely unique within individual cell populations. The mechanism that allows a particular cell type to acquire its function is related to what parts of the whole genome are exposed to the transcriptional machinery and hence define cell type specific identity. The term epigenetics (the prefix *epi-* derived from Greek for "over" or "above") was coined by Conrad Waddington in the 1940s and referred to the processes by which a particular genome is able to construct and maintain a proteome whose overall biological properties form the underlying basis of life [74]. Over the past decade, the term epigenetics has been adopted to define mechanisms that control chromatin remodeling and the accessibility of genes to transcriptional machinery. The total length of DNA in a single somatic cells exists in the nucleus in complex with histone proteins that have been described as a highly compressed structure referred to as chromatin. The primary structural unit of chromatin is the nucleosome, which comprises a standard length of DNA (147 base pairs) wrapped around a histone octamer make up of four pairs of basic histone proteins (H2A, H2B, H3 and H4). The structure and organization of chromatin depend on covalent modifications known as epigenetic factors that include DNA methylation and histone modifications that occur principally on their N-tails. In vertebrates, methylation of CpG dinucleotides within proximal gene promoters is frequently linked to transcriptional repression (Fig. 1) [75]. Some of the histone

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