



Review Article

Epigenetic control of the GABAergic interneurons migration and NMDA receptor functioning in schizophrenia.

Control epigenético de la migración de interneuronas GABAérgicas y funcionamiento del receptor NMDA en la esquizofrenia.

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Abstract

Schizophrenia is a polygenic condition whose etiology remains unknown. Recent research highlights the GABAergic interneuron migration and the NMDA receptor hypofunctioning as two attractive hypotheses of its molecular basis; however, none of them explain all the anatomical and clinical abnormalities found in schizophrenia when considered separately because, although it is a neurodevelopmental disorder, the onset traditionally appears in the adolescence and is preceded by a period of normality, suggesting that there is more than one molecular mechanism and that they are all governed by common factors. Reelin, Neuregulin I (Nrg1) and Brain Derived Neurotrophic Factor (BDNF) have been linked to schizophrenia and they have three common features: their involvement in the GABAergic interneuron migration and in the proper functioning of the NMDA receptors and that they are all subject to similar epigenetic control.

Key words: Schizophrenia, Epigenetic, Neuronal migration, NMDA hypofunction, GABAergic interneurons.

Resumen

La esquizofrenia es una condición poligenética cuya etiología permanece desconocida. Investigaciones recientes resaltan la migración de interneuronas GABAérgicas y la hipofunción del receptor NMDA como hipótesis atractivas sobre sus bases moleculares; sin embargo, al ser consideradas por separado, ninguna de ellas termina de explicar todas las alteraciones neuroanatómicas y clínicas de la enfermedad ya que, a pesar que la esquizofrenia es considerada una patología del neurodesarrollo, el debut del cuadro se produce al inicio de la adolescencia y está precedido por un período de normalidad, lo que sugiere que existe más de un mecanismo molecular, controlados todos por factores comunes. La Reelina, Neuregulina I y el BDNF han sido moléculas extensamente vinculadas con la esquizofrenia que comparten tres características: Intervienen en la migración de interneuronas GABAérgicas y en el correcto funcionamiento del receptor NMDA y están sujetas a un control epigenético similar.

Palabras clave: Esquizofrenia, Migración Neuronal, Hipofunción del receptor NMDA, Interneuronas GABAérgicas.

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I. Introduction.

Neuronal migration refers to an extremely complex process that involves hundreds of molecules which mediate the necessary events for neurons to leave their primary location in the fetal brain and move towards their exact adult brain location, where they will exert an inhibitory role. After performing a tangential migration from the ganglionic eminences, GABAergic interneurons undergo a second radial migration process in order to reach their final position in the cerebral cortex. Many genes linked to schizophrenia regulate both tangential and radial migrations, thus justifying the reduction of interneurons observed in the prefrontal cortex of schizophrenic patients.¹ Neuronal migration occurs in three sequential steps: 1) leading edge extension, 2) nuclear translocation or nucleokinesis, and 3) retraction of the trailing process; these steps are mediated by genes whose expression depends on a fine epigenetic control and, consequently, the success of the migration process. Once located in the cerebral cortex, interneurons must integrate into specific brain circuits and establish negative feedback loops with pyramidal neurons. When those synaptic connections become abnormal, interneurons will produce a poor inhibition of pyramidal neurons with a subsequent hyperactivity which, in theory, would explain the psychotic symptoms of schizophrenia.² The best experimental study supporting this hypothesis was conducted in healthy subjects undergoing an NMDA receptor antagonist to reproduce schizophreniform symptoms.³ In theory, both a deficit of GABAergic interneurons and an NMDA hypofunction would generate a cortical disinhibitory state

that could cause the schizophrenic psychosis, being epigenetic control of these processes the most reasonable neurophysiological approach to explain the genesis of these alterations.

The term “epigenetic” refers to chromatin modifications without an alteration of the structural DNA sequence, which results in gene expression changes. Contributing factors to epigenetic regulation include microRNA,⁴ DNA methylation⁵ and post-transcriptional histone modification⁶ DNA methylation is a chemical modification to cytosine to form 5-methylcytosine, this results in a reduction in the accessibility of transcription factors to DNA depending on methyl donors, methyltransferases (DNMT) and S-adenosyl methionine (SAM). Histone acetylation facilitates gene transcription; a process carried out by histone acetyl transferases (HATs) and reversed by histone deacetylases (HDAC). BDNF, Reelin and Nrg1 are three of the several genes linked to schizophrenia and they are involved in the GABAergic interneuron migration and in the proper functioning of the NMDA receptors (Fig. 1), they also share at least one epigenetic mechanism of gene transcription. Then, does schizophrenia involve a deficit of interneurons in the cerebral cortex, established during neurodevelopment, which later requires a hypofunctioning of the NMDA receptors to trigger the onset of the disease? Is the integration of those events determined by epigenetic alterations triggered at different times in life? This article will review the role of BDNF, Reelin and Nrg1 on the interneurons migration and the NMDA function, as well as their mechanisms of epigenetic control.

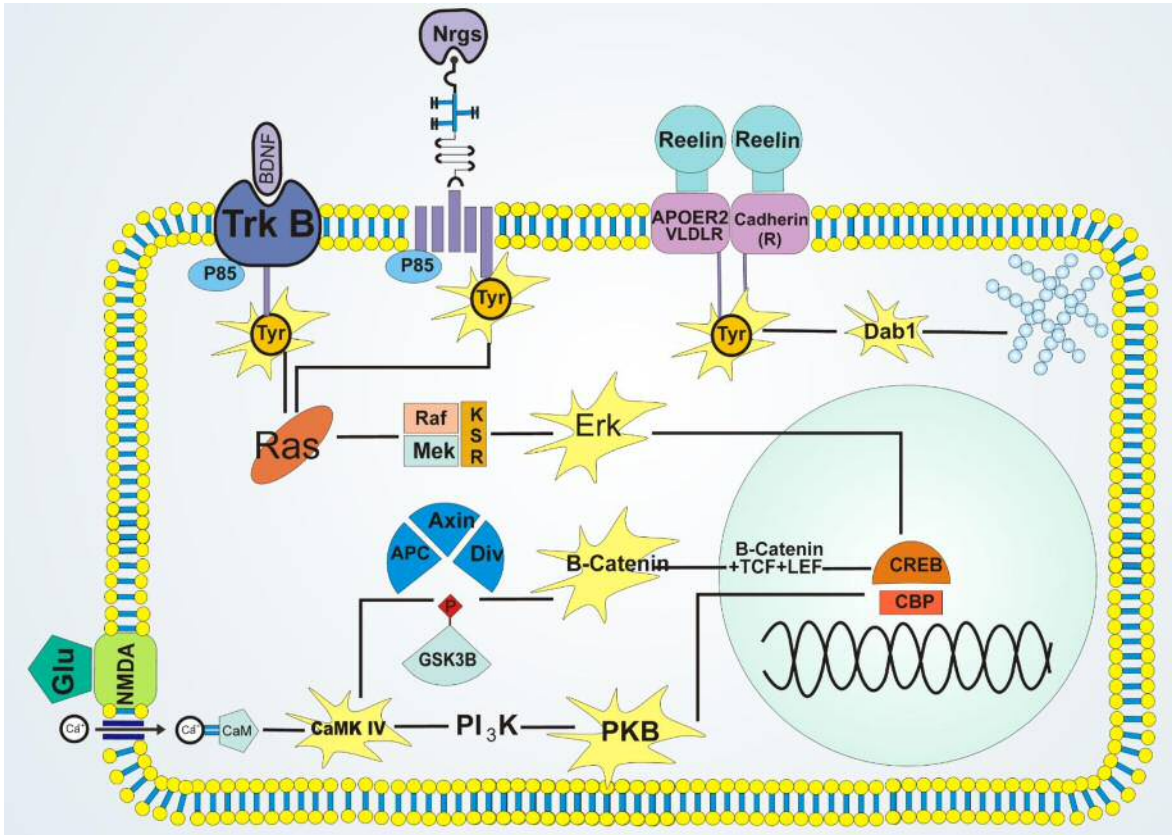


Figure 1. BDNF, Reelin and Nrg1 intracellular effects in GABAergic interneurons migration. BDNF activates the RAS/RAF signaling pathway and produces ERK, promoting gene transcription through CREB in the cell nucleus. Nrg1 has a similar intracellular effect. NMDA activation on the cell membrane produces a calcium influx that activates Calcium calmodulin Kinase IV (CamK IV), phosphorylating Glycogen synthase Kinase 3B (GSK3B) and allowing B-catenin to activate CREB. Reelin promotes the neuronal cytoskeleton reorganization, a key event in neuronal migration, through Dab1.

2. GABAergic interneurons migration.

The migration of interneurons is a complex process mediated by the expression of hundreds of genes in a synergistic way that not only ensures a proper migration, but also a complete maturity in order to achieve a correct inclusion into the inhibitory circuitry. BDNF expression is important for the interneurons migration to the cerebral cortex during development and the early postnatal stage.⁷ In knockout mice for the BDNF receptor TrkB, there is a decrease of interneurons during tangential migration in the embryonic period.⁸ Once the tangential migration is completed, GABAergic interneurons in the cortex need other extracellular elements to perform the radial

migration process. These elements are mainly represented by Reelin and Radio-glia cells.

Reelin is a glycoprotein secreted by Cajal-Retzius cells and binds to specific receptors in the interneurons cell membrane and promotes radial migration.⁹ Studies with knockout mice for the reelin gene show the importance of this molecule in the laminar configuration of the cerebral cortex. Younger neurons usually stop their migration in deep layers while adult neurons do it in superficial layers. In a knockout mice model for this gene this process is reverted¹⁰; thereby, despite the interneuron radial and tangential migrations are not affected directly, interneurons arrive to a wrong

place because the cerebral cortex blades are inverted.¹¹⁻¹³

Nrg1 is a family of extracellular growth factors that requires the expression of the ErbB receptor on the interneuron cell surface during migration. Nrg1 activates the ErbB receptor and triggers the extracellular receptor Kinase (ErK), a second messenger cascade culminating with the activation of a wide range of transcription factors. Mutations to Nrg1 or ErbB genes not only induce a migration failure, but also a reduction in the number of interneurons in the cortex¹⁴ and hippocampal tissue.¹⁵

3. Synaptic connection and NMDA hypofunction.

The ionotropic NMDA receptor has been postulated as a target for schizophrenia due to the observations made with phencyclidine, a noncompetitive blocker of these receptors, which produces psychotic symptoms similar to those experienced by schizophrenic patients.³ NMDA antagonists induce both positive and negative schizophrenic symptoms as well as the cognitive impairment associated with the disease. The NMDA receptor is a heteromeric molecule composed of at least one NR1 subunit coupled to different combinations of NR2 subunits and /or NR3.¹⁶ The Grin1 and Grin2 gene expression produces different combinations of NR1 subunit with four different types of NR2 subunit (NR2A-D) and two types of NR3 (NR3 A-B), forming a multitude of NMDA receptors with different phenotypes and biophysical properties as well as different patterns of expression in the mammalian brain during development and adulthood.¹⁷ BDNF has emerged as a major regulator of synaptic transmission and

plasticity in the adult brain, with a TrkB distribution mainly at glutamatergic synapses. BDNF promotes the expression of synaptobrevin and synaptophysin (proteins associated to synaptic vesicles) in the presynaptic region, an effect also exerted by TrkB (Fig. 2).¹⁸⁻¹⁹ Some of synaptic effects of BDNF are achieved through the activation of MEK-ERK signaling pathways which in turn activate the CREB transcription factor and promote Arc production²⁰; this promote synaptic plasticity when establishing a contact with actin filaments, resulting in expansion of the postsynaptic region and the expression of both NMDA and AMPA receptors.²¹

Reelin increases phosphorylation of the NR2A subunit, thus improving NMDA performance.²² Recent findings indicate that reelin exposure affects the AMPA receptor functioning through several mechanisms resulting in both presynaptic plasticity and a more efficient regulation of glutamate presynaptic release.²³ Reelin is necessary for NMDA maturation during postnatal development and promotes AMPA expression at the synaptic surfaces; it also reduces silent synapses in hippocampal tissue.²³ Furthermore, reelin dramatically increases the long-term potentiation induced by high frequency stimulation, a phenomenon which occurs when reelin activates its ApoER2 and VLDLreceptors.²⁴ Nrg1 also phosphorylates the NR2A subunit of the NMDA receptor, a process decreased in the brain of schizophrenic patients.²⁵ In fact, it is known that ErbB4 has direct contact with both NR2A and NR2B, and its location appears to be exclusive to synaptic connections where these molecules exist (Fig. 2).²⁶⁻²⁷

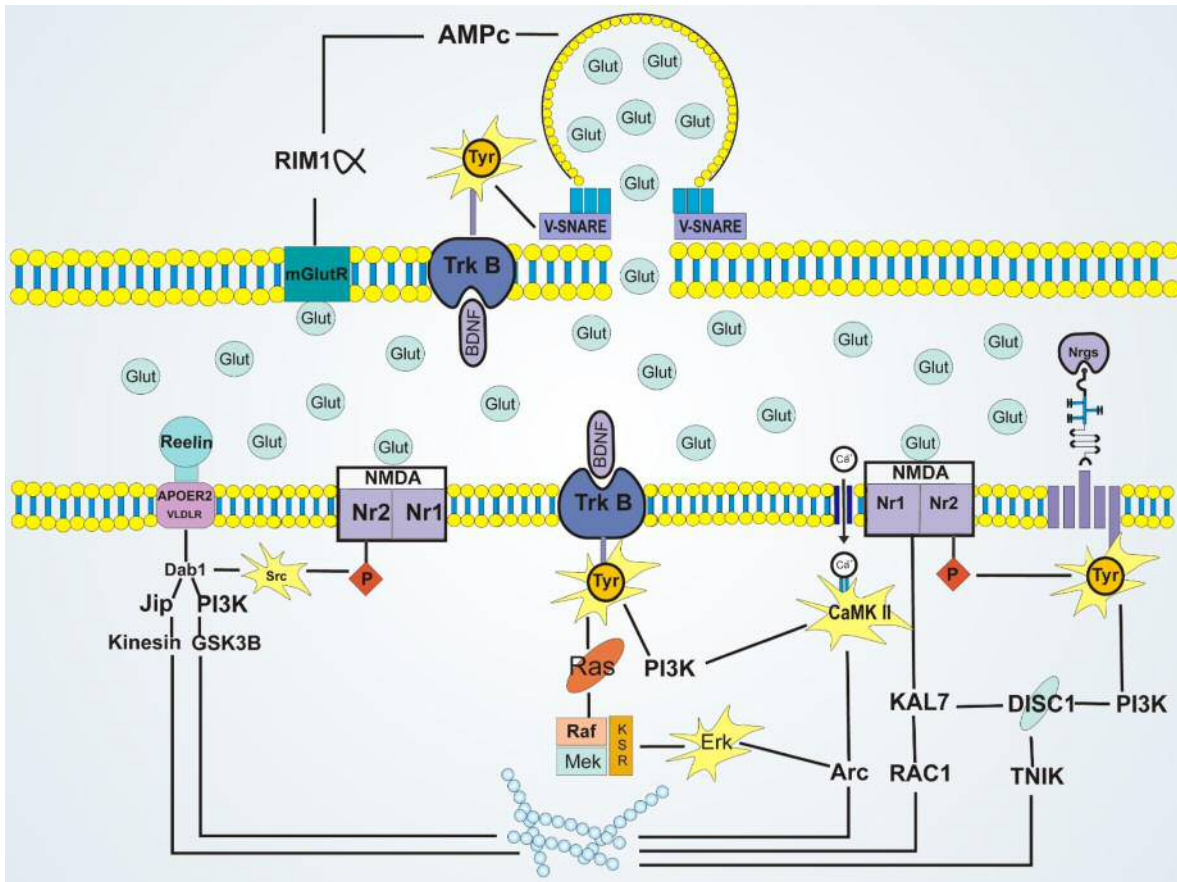


Figure 2. BDNF, Reelin and Nrg1 effects in glutamatergic synapses. BDNF promotes V-SNARE expression at the presynaptic region, this is a family of proteins which regulates side and glutamate amounts within synaptic vesicle. In the postsynaptic region BDNF activates ERK which promotes cytoskeleton reorganization through Arc, thus expanding the postsynaptic surface and increasing AMPA and NMDA expressions. Reelin phosphorylates the NR2 subunit through Src, improving its performance. Moreover, through Kinesin and GSK3B expression, Reelin promotes cytoskeleton reorganization. Nrg1 also phosphorylates the NR2 subunit and promotes cytoskeleton reorganization through Disrupted in Schizophrenia I (DISC1), TRAF2 and NCK interacting kinase (TNIK).

4. Epigenetic.

Epigenetics of schizophrenia represent the only mechanisms linking almost completely every molecular alteration described for this disorder. DNMT1 is increased in the cytoplasm of cortical GABAergic interneurons of psychotic patients (schizophrenics and bipolar)²⁸ and haloperidol induces histone 3 phosphorylation, thus promoting gene transcription.²⁹ In addition, CBP (CREB binding protein), a structure located in promoter regions, recruits CREB for the transcription of many molecules associated

to schizophrenia and induces histone acetylation itself, also promoting gene transcription.³⁰

The BDNF, Reelin and Nrg1 genes have been studied from many different perspectives related to the molecular origins of schizophrenia, allowing us to find similarities between them. These three genes are involved in the interneurons migration and in the proper functioning of the NMDA receptors, they have more than three promoter regions and at least one of these regions is transcribed by CREB; moreover, they share a similar epigenetic control

involving common molecules for their transcriptional regulation.

BDNF is a complex gene of four promoter regions producing at least eight different mRNAs. In rodents, an increase in the exon 4 methylation leads to decreased mRNA expression in the prefrontal cortex,³¹ a finding identified in schizophrenic patients.³² Zebularine, a demethylating agent widely used for cancer treatment, triggers changes to the exon-specific BDNF mRNA levels in rodents indicating that an altered DNA methylation is sufficient to drive the differential BDNF transcript regulation in the hippocampus.³³ The BDNF exon 3 has an epigenetic control dependent of the degree of synaptic activity. Membrane depolarization and the subsequent intracellular calcium influx promote MeCP2 phosphorylation and a separation of the methyl group, thus promoting their transcription.³⁴ The BDNF exons 1 and 4 show a transcriptional control by histone 3 in the prefrontal cortex³⁵ that has been directly linked to schizophrenia. MAPK/ERK, a molecular cascade linked to the disease, phosphorylates histone 3 favoring the arrival of transcription factors to DNA.³⁶ In addition, synaptic activity promotes the separation of MeCP2 from CoRE1 silencing transcription factor (CoREST), a molecular complex that inactivates gene transcription (Fig. 3).³⁷

Reelin gene structure contains 65 exons spanning 450kb of DNA. Its transcription result in a 12kb RNA and a 3461 amino acids protein mainly expressed in interneurons.

Reelin has four potential sites for transcriptional regulation (SPI, NF-KB, CREB, and CpG). SPI and CREB showed a hypermethylation by DNMT1 in schizophrenia,³⁸ which explains reduced expression of Reelin in the prefrontal cortex of schizophrenic patients.³⁹ Other known mechanisms of Reelin epigenic regulation are SAM and MeCP2. SAM donates methyl groups to DNMT1 to execute the CpG methylation process. MeCP2 is recruited by methyl groups and adopts HDAC to remove the acetyl group from histones.

Finally, Nrg1 gene has nine exons producing at least 15 mRNA isoforms. It has a length of 1.4 Mb from which only about 0.3% encodes proteins. The variety of functions and complex expression mechanisms from development to adulthood can be explained by its large number of promoters,⁴⁰ among which c-Fos, CREB and SPI stand out. Although it is assumed a broader epigenetic control of the Nrg1 gene from the environment, this mechanism remains misunderstood; however, there is evidence for Nrg1 epigenetic in breast tissue, where it executes a protective effect against tumor formation. In fact, hypermethylation of Nrg1 leads to breast cancer;⁴¹ this may be the explanation for the higher incidence of breast cancer amongst schizophrenic women.⁴² Methylation specifically occurs in exon 2,⁴³ and other promoter regions such as NFKappaB and SPI show a similar epigenetic regulation (Fig. 3).⁴⁴

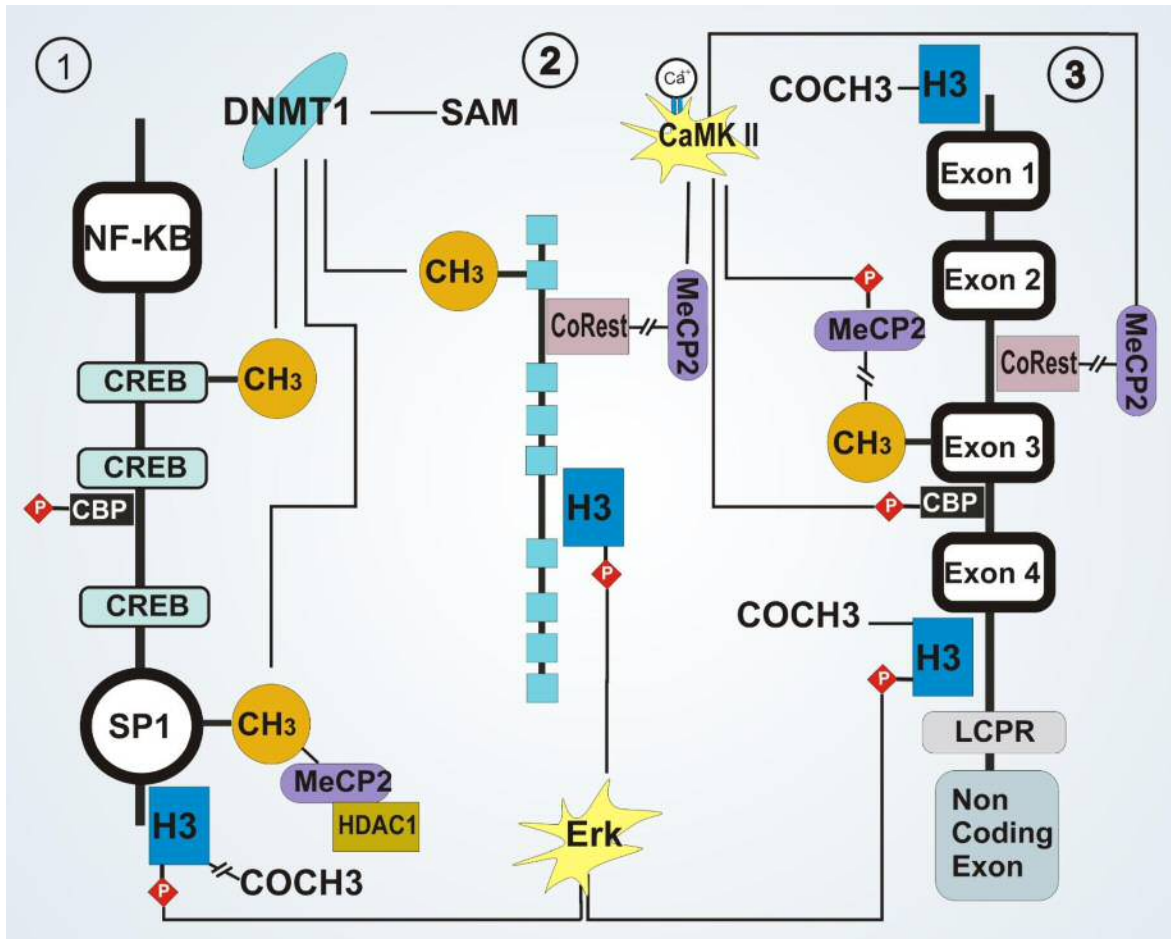


Figure 3. Epigenetic regulation of BDNF, Reelin and Nrg1 in schizophrenia. 1. Reelin gene is methylated by DNMT1. Methyl groups recruit MeCP2 and HDAC1 avoiding histone acetylation and reducing gene transcription. Calcium influx induces CBP phosphorylation, improving gene transcription by CREB. ERK phosphorylates histone 3, retaining the acetyl group and improving gene transcription. 2. The Nrg1 gene presents CpG methylation and histone 3 phosphorylation by ERK. 3. The BDNF gene presents a reduction in transcription by CoREST silencing transcription factor (CoREST) which needs MeCP2 binding to exert its effect. Calcium separates MeCP2 from CoREST, improving gene transcription. Moreover, Calcium phosphorylates CBP, improving gene transcription by CREB.

5. Conclusions and future questions.

Molecular and genetic findings have opened the possibility for an approximation to the pathogenesis of schizophrenia; however, when we evaluate a particular gene effect, we understand that each gene linked to schizophrenia has a minimal effect on a common physiopathological process and does not justify the main changes postulated for this disease by itself. Epigenetic comes to unify many of the hypotheses that remain

unconnected. For example, two of the most significant findings concerning the molecular biology of schizophrenia are a deficit of GABAergic interneurons in the prefrontal cortex and a NMDA hypofunction. To be assessed separately, none of these findings justify the spectrum of abnormalities occurring during the course of the disease because a deficit of interneurons refers to a set of processes having place in the prenatal and early postpartum stages,⁴⁵ while synaptic connection alterations appear to occur later

in the life of a schizophrenic subject. A reasonable explanation would be the hypothesis that the glutamatergic system undergoes through a period of maturity with a significant change in the NMDA receptor conformation when adulthood begins,⁴⁶ a period in which many schizophrenics present the onset of the psychotic symptoms,⁴⁷⁻⁴⁸ Abnormalities in the epigenetic regulation of Reelin, Nrg1 and BDNF presumably are present since the beginning of the schizophrenic subject's life, justifying the lack of interneuron migration in the prefrontal cortex and the NMDA hypofunction. Such changes would be clinically relevant after the glutamatergic system maturation, when the prefrontal dishinibitory state is finally established. However, this approach suggests new questions: if some exons linked to schizophrenia have a direct relation with second messengers present in both the synaptic connection and the interneuron migration (calcium, calmodulin and MEK) and the epigenetic processes are positively or negatively affected by them, is gene expression thereby the cause or consequence of such phenomena? And, is the epigenetic regulation during the prenatal and adult stages the same? The discovery of multimolecular complexes such as RE1 silencing transcription factor (REST), present only during neurodevelopment with an extensive epigenetic control over genes linked to schizophrenia, makes us understand that there is still a long way to decipher the molecular origins of this disease.

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