

Epigenetic and Genetic Aberrations of the Brain Dopaminergic System in Schizophrenia and Bipolar Disorder: Achievements and Prospective

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The molecular mechanisms of the fact that more than 50% of the individuals with the same genetic make up (e.g. identical twins in schizophrenia) do not show the same psychiatric phenotype remained undefined in psychiatry. This along with the failure to find responsible genes with major effects in psychiatric disorders and lack of consistency of genetic association studies led to the current unanimous conclusion that, in addition to the genetic factors, environmental and epigenetic factors influence the functions of brain and the presentation of the symptoms in mental diseases. Here we reviewed the potential epigenetic dysregulations of genes related to dopaminergic (DAergic) system. A comprehensive genetic and epigenetic analysis of the DAergic and the interacting pathways such as serotonergic and glutaminergic systems could help to understand the molecular bases of the differences in disease severity in individuals with similar or identical genetic make-up that can assist for the identification of novel targets with therapeutic and preventive applications.

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In human only 3% of the DNA bases code for proteins. The rest of the DNA is involved in preserving the structure and integrity of chromosomes and regulation of genes functions in interaction with other genes and environment (1). Approximately 1/3 of the human 30,000 genes are expressed in the brain that mostly synthesize structural proteins, while others encodes enzymes, receptors, and neurotransmitters required for normal brain functions in different developmental periods and environmental conditions (2). Though the genetic make up establishes the primary neuronal structures and connections, environmental interactions play a significant role in the modification and fine-tuning of these connections for

adaptation (1-4). In fact, genes which are involved in the production of enzymes, receptors and neurotransmitters have continuous interaction with the environment to produce appropriate amount of these materials for that environmental condition. Interestingly, environmental interactions somehow are memorized in genes developmental memory, so that this memory can influence the response of the genes in the next exposures (5-7). It was shown that epigenetic mechanisms, in general, and DNA-methylation, in particular, are the main underlying mechanisms for memorizing the environment exposures at cellular level (6-9).

As reviewed elsewhere (10) DNA-methylation is carried out by the addition of a methyl group (CH₃) to cytosines which are followed by guanine (C-G) by mediation of DNA methyltransferase (DNMT) enzymes. Choline is the main resources of methyl group and S-adenosyl methionine (SAM) is the major methyl donor, while folic acid and vitamin B12 are necessary for recruitment of the demethylated SAM (11,12).

Indeed, the four bases of DNA are fixed and can provide a long-term memory for inheritance, but methyl groups are flexible/

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dynamics and adapt to different external conditions to fine tune genes expression in a specific tissue for a specific time in each generation that the genome is not able to make in the short-term (9). There is a dynamic change in DNA-methylation level according to the critical periods of development and the environmental conditions (13-15). In addition to DNMTs, the presence of essential nutrients/resources such as folic acid, methionine and choline that determine the availability of methyl groups play a crucial role for a proper establishment of the DNA-methylation level (14-16). Diverse nutritional or environmental factors such as butyrate, alcohol (17-19), tea polyphenols (20), hypoxia, nitric oxide, hormones (10) and arsenic (21) may also alter methylation patterns of genes. Because DNA-methylation pattern is generally retained during cell division, any DNA-methylation alterations could affect all progenies of the affected cells. However, depend on the developmental periods as well as the locality of the exposure to noxious agents these effects could be site specific, affecting only specific genes in specific cells or tissues (6,7,9).

Although all cells of an organism have a same genetic make up, during cells differentiation each tissue and even each cell acquires its own heritable but potentially reversible DNA- methylation pattern establishing its identity and functions for the future (6,7,9). Environmental stimuli mediated by several elements/factors (e.g. neurotransmitters, hormones and transcription factors) can modulate genes methylation and expression levels along the life of each organism for adaptation to that environment (6,7,9,10). For instance, the release of dopamine (DA), nor-epinephrine and serotonin in response to environmental stimulations can activate several genes to produce specific structural or regulatory proteins to deal with that condition. Those synapses that have been conditioned by these catecholamines become subject for the influence of these protein that mediate growth, synaptic consolidation and long-lasting structural changes (3,4). For instance, BDNF is among the proteins that are produced as a result of neuronal activation

which play prominent roles in the neuronal growth, connectivity and functionality. This process is launched after DRD1 stimulation and the release of c-AMP and cyclic AMP response element binding protein (CREB) which could alter BDNF promoter DNA-methylation level at CRE binding site and increase expression level inducing long lasting structural changes (22-25). As reported in mice, even the style of maternal care could change DNA-methylation pattern of the glucocorticoid receptor gene in the offspring's hippocampus which could maintain until adulthood (26). Interestingly, successive bindings of transcription factors to a gene's regulatory regions, induced by environmental stimuli, decrease DNA-methylation level and increases the capacity of gene expression in the future (8,27). This could be the underlying mechanism for "kindling" which is highly likely responsible for the relapse of mood disorders upon stress or cyclic environmental conditions.

Genetic and epigenetic alterations of the DAergic system in schizophrenia (SCZ) and bipolar disorder (BD)

While there have been more than 1000 genetic studies that focused on the analyses of genetic polymorphisms in psychiatry, there has been no success in identification of any gene with major effects in major psychiatric diseases (13). The fact that most of the psychiatric diseases have an episodic nature and spontaneous remission suggests that genetic mutations alone are not responsible for diseases phenotype, as they could not be spontaneously recovered, for example in mood disorders. However, a disturbed epigenetic fine tuning of the expression of responsible genes can explain the episodic nature of psychiatric diseases.

Although it is becoming three decades that the concept of epigenetics was introduced to the field of medicine, research on the potential role of epigenetics in the pathogenesis of mental diseases is in its beginning in psychiatry. Current achievements in the role of epigenetic aberrations in mental diseases include hypermethylation of reelin (28,29) and SOX10 (30) in SCZ, hypomethylation of the

MB-COMT promoter in SCZ and BD (31), global hypomethylation of leukocyte DNA in male SCZ(32) hypomethylation of GAD1 promoter, associated with gene hypo-expression in SCZ (33) and hypomethylation of PPIEL (peptidylprolyl isomerase E-like) in patients with bipolar II disorder (34). Other studies also reported hypermethylation of genomic DNA for alpha synuclein (17) and HERP promoters in alcoholism (19), hyper-expression of DNMT1 (35,36) and increase in SAM content in cortical inter-neurons of patients with SCZ and psychotic BD (37).

This review is focused on methylation, transcriptome and polymorphisms of DAergic genes involved in the pathogenesis of major psychiatric disorders in an integrated approach. For selection of the candidate genes this work was reliant on pharmacological evidence and genetic association studies confirmed by meta-analyses to make a more reliable conclusion for preventive or therapeutic interventions.

Dopamine (DA): production, degradation and functions

DA is produced from tyrosine by mediation of tyrosine hydroxylase (TH) enzyme (38). In human embryos TH-immunopositive cells are detected at 5-6 weeks of gestational age and distinct DA neuritic processes begin to extend by 8 weeks (38). DA is involved in many developmental processes and brain activities including attention, executive memory, cognition, emotional behavior and natural rewards. These effects are mediated by a cascade of cell signaling events involving DRD1 and DRD2-like receptors that act on downstream pathways (1-5,38). Additionally, dopamine transporter (DAT1) reuptakes and recruits the DA from the synaptic cleft (1,5,38).

DA is also an intermediate product for biosynthesis of nor-epinephrine (NE), by mediation of dopamine beta hydroxylase (DBH) enzyme. NE is an important neurotransmitter/modulator involved in mood regulation and neurodevelopment (38).

Based on pharmacological studies dysfunction of sub-cortical and cortical DAergic and NEergic systems of the brain are involved in the pathogenesis of SCZ and

mood disorders (1,5). There is a close interaction between DAergic neurons of the frontal lobe and sub-cortical region and this interaction is required for fine-tuning of both cortical and sub-cortical DAergic system (39,40).

It is believed that alterations in the sub-cortical DAergic systems of patients with SCZ may be secondary to a primary hypo-function of DAergic system of the prefrontal cortex (1,39-41). Further support was provided by human studies as hypo-function of the prefrontal cortex in SCZ was correlated with increased striatal DA release (42). On the other hand, studies with the D2 transgenic mice showed that a primary abnormality of the sub-cortical DA system (selective over-expression of DRD2 in the striatum) could cause persistent abnormalities in prefrontal cortex functioning (43). Therefore, although the lack of inhibitory effects of the frontal lobe DAergic neurons over sub-cortical region may result in an outrage of mesocortical DAergic activities and psychotic phenotype (39,40), hyper-expression of DRD2 in striatum could also impact the functionality of frontal lobe DAergic system in a vicious cycle.

MB-COMT: a brief review of genetic and epigenetic findings in psychiatry

A comprehensive review on the genetic polymorphisms of COMT that influence the homeostatic levels of DA in the synapses is provided elsewhere(31). In brief, COMT gene is located in 22q11.21 chromosomal region that is linked to SCZ and BD. In humans a mutation at codon 158 of MB-COMT that predominantly degrades the synaptic DA in human brain created a functional polymorphism with substitution of methionine (Met) instead of valine (Val) in the COMT enzyme. The Val allele has three times higher physiological activity compared to the Met allele. The increased DA degradations resulted from the Val allele is associated with a progressive disturbance in attention, executive cognition, and working memory performance in normal individuals as well as schizophrenic patients, while the Met allele is associated with greater stability in

performance and less variability in reaction time.

In spite of several reports indicating an association between the Val allele and the risk for SCZ and BD as well as early onset major depressive disorder and suicide, meta-analyses of the published studies in SCZ and BD provided contradictory results. This suggests that in addition to genetic polymorphisms, environmental and/or epigenetic factors may also determine COMT functions confounding the effects of the risk allele.

These backgrounds promoted an analysis of MB-COMT promoter methylation status and Val/Met polymorphism in 115 post-mortem brain sample provided by the Stanley Medical Research Institute and The Harvard Brain Tissue Resources Center to combine genetic and epigenetic data in correlation with the role of gene-environmental interactions in an integrated model. These studies provided strong evidence for over-activity of the MB-COMT in the frontal lobe of patients with SCZ and BD (31). For instance, there was a higher level of MB-COMT expression associated with higher frequency of hypomethylation of the gene promoter in SCZ and BD versus controls (methylated=26% and 29% vs. 60%; $p=0.005$ and 0.008 , respectively), particularly in the left frontal lobe (31% and 30% vs. 81%, $p=0.004$).

There was also a tendency for the enrichment of the Val allele with MB-COMT hypomethylation in the patients as 87% of the samples who were homozygous for Val and had an unmethylated MB-COMT promoter were among SCZ and BD patients versus 13% in controls. In contrast, only 18% of the samples homozygous for Met and a methylated MB-COMT promoter were among SCZ or BD patients versus 82% in controls. Similarly, there was a significant association between suicide and genetically or epigenetically determined COMT hyperactivity (Val homozygosity and MB-COMT hypo-methylation) in BD (31). In fact, there were no cases with Met homozygosity and a methylated MB-COMT promoter among all suicidal patients including schizophrenics.

These studies also revealed that Val homozygosity of COMT was associated with RELN gene (involved in neuronal migration and synapse formation) promoter DNA hyper-methylation ($P=0.01$). An inverse correlation between MB-COMT expression and the level of expression of DRD1 (31), DRD2 and RELN was also detected (44). All together, these data strongly suggests that Met homozygosity and/or MB-COMT promoter methylation may be protective against SCZ, BD and suicide while Val homozygosity and COMT hypo-methylation are associated with the diseases phenotypes.

Despite these studies that uncovered a distinct profile of differential epigenetic aberration of a number of genes (MB-COMT, DRD2 and RELN) in SCZ and BD, there are several other interacting genes remain to be examined. For example, MAOA and DAT1 also degrade or reuptake DA (respectively) affecting the synaptic DA level. Furthermore, while the expression of DRD3 is dependent on the DA availability in the frontal cortex (45), DRD3 in turn modulate TH expression and regulate DA level (46) likely through epigenetic mechanisms. Similarly, in mice lacking the DRD2 (D2R^{-/-}) the number of mesencephalic cells containing TH is significantly low during ontogeny compared to the wild-type (47). Hence, DRD3 and/or DRD2 under-stimulation due to insufficient synaptic DA resulted from MB-COMT hyperactivity may have the same effects on TH expression influencing the development and functionality of the brain DAergic system. Therefore, defining both the promoter methylation status and gene polymorphisms of these and other related genes will help to understand the magnitude of frontal lobe DAergic dysfunction and the role of gene-gene interactions in SCZ and BD pathogenesis. Here, a brief review is presented to describe the potential impacts of epigenetic alterations of these interacting genes.

Monoamine Oxidase A (MAOA)

Several studies indicate that MAOA dysfunctional polymorphisms may be involved in the pathogenesis of major mental

disorders (48). However some genetic studies showed contradictory results in the association between polymorphism of MAOA and SCZ or mood disorders (49,50), multi-center studies and meta-analyses support such associations (51-54). As the epigenetically determined hyperactivity of MB-COMT could be secondary to MAOA hypo-activity or could be intensified by concurrent MAOA hyperactivity, an analysis of MAOA expression and promoter methylation levels is required to pool the data of these studies to define the level of contribution of each player and the magnitude of brain DAergic dysfunction in SCZ and BD.

Tyrosine Hydroxylase (TH) and Dopamine hydroxylase (DBH)

TH catalyzes the first and rate limiting step in the synthesis of DA from tyrosine. DA could be employed directly or converted to NE by mediation of DBH. Thus any problem in DA production due to TH dysfunctional polymorphism and/or DNA-methylation aberrations would impact NE biosynthesis as well. Some polymorphisms (e.g. C-1021T) of DBH (55-57) have functional effects as are associated with lower levels of NE production and subsequently an elevated level of the brain DA due to the lower conversion of DA to NE (58). Hence, it was hypothesized that non-genetic and genetic dysfunction of DBH gene could be related to both depressive and psychotic phenotype (56,59). As depressive phenotype is closely associated with a low NE level and NE production is related to TH and DBH activities, further studies are required to uncover whether the TH and DBH promoters are differentially methylated in SCZ or BD. It would be also helpful to define the functional polymorphism of DBH to poll epigenetic and genetic data in an integrated model to explain the disease pathogenesis.

Dopamine receptor type-3 (DRD3)

According to meta-analyses DRD3 genetic polymorphisms are associated with SCZ pathogenesis (60,61). As discussed above, however the expression of DRD3 is dependent on the DA availability in the frontal cortex (45), pre-synaptic DRD3

involves in the regulation of synaptic DA as well as the expression of TH (46). These data along with the presence of a cAMP response element (CRE) in TH promoter and the fact that DRD2 knockout mice show TH under-expression (47) suggest that stimulation of pre-synaptic DRD2 and/or DRD3 influenced by synaptic DA level may modulate the TH methylation/expression level through a cascade of events that finally act on the CRE of TH promoter. Any impact on TH expression may also lead to a change in NE level that is produced from DA. Therefore, the synaptic DA deficiency may lead to the development of a vicious cycle that the final outcome of this condition is the lack of fine-tuning of CRE methylation in TH promoter and subsequent changes in neuronal DA/NE production and the corresponding clinical phenotypes such as cognitive deficits, depressed mood and negative symptoms.

Furthermore, since in the pre-synaptic neurons DA is mostly stored in the vesicles, unlikely this source of DA could be used for NE production. However, the re-up-taken DA by DAT1 could be recruited for NE production by mediation of DBH enzyme. Assuming that the released DA to the synaptic cleft is extensively degraded by hyperactive MB-COMT and/or MAOA, the efficiency of DAT1 for reuptake/recruit of the remnant DA would be compromised in the frontal lobe, where DAT1 shows low level of expression. This conclusion is consistent with other observations addressing that the frontal lobe dopaminergic system is hypoactive in SCZ and other major psychiatric diseases.

Dopamine receptor type-4 (DRD4)

Although one meta-analysis reported that promoter polymorphism of the DRD4 was not associated with SCZ (62) another meta-analysis found ethnic heterogeneity among the studies and reported an association between the long form of DRD4 gene and SCZ in Caucasians (63). An association between DRD4 exon3 variants and delusional symptomatology in major psychoses was also reported (64). Another meta-analysis reported an association between DRD4 polymorphisms and mood disorders as well (65). DRD4 is a

member of DRD2-like receptors which has some unique properties making it a prior candidate for genetic/epigenetic analyses. One report indicates that the DRD4 gene, located on 11p15.5 chromosomal region and in close proximity to a cluster of imprinted genes, is linked to BD and exhibit parent of origin (maternal) effect (66). This suggests that DRD4 abnormal genomic imprinting, a known epigenetic event, may be involved in BD pathogenesis. DRD4 has intra-neuronal cytoplasmic distribution (67) and in interaction with folic acid modulates cellular methylation processes (68) so may contribute in DNA methylation processing as well (10).

Discussion and therapeutic application

Based on recent findings activation of different forms of DA receptors in the frontal lobe depends on the synaptic DA level (69). Any decline in synaptic DA level first may lead to under-stimulation of DRD2 which generally inhibits cAMP signaling events (1). In the next step, by more decrease in DA level, DRD1 (that generally stimulates cAMP signaling) will not be efficiently stimulated as well. In this condition the coordinated regulation of cAMP signaling mediated by DRD1 and DRD2 is compromised. Thus, by inactivation of the critical players for on/off tuning of the neurons the affected cells are functionally dissociated from the neuronal network. This partial isolation may cast the information processing required for abstract thinking, normal cognition and judgment. In addition, cAMP dependent genes promoters such as BDNF and RELN may become methylated and under-active in this situation.

Furthermore, the frontal lobe synaptic DA deficiency and under-stimulation of pre-synaptic DRD3 (and possibly other DA receptors) may also lead to the development of a vicious cycle that the final outcome of this condition is the lack of fine tuning of CRE of TH and/or DAH genes and their subsequent promoter DNA-methylation changes leading to dysregulation of neuronal DA/NE productions and the corresponding clinical symptoms such as cognitive deficits, depressed mood and negative symptoms.

Since DA deficiency resulted from the genetic hyperactivity of COMT (Val allele) is associated with an increased TH expression in the mesencephalic DA neurons (70), epigenetic- determined brain DA deficiencies may also activate a feedback mechanism which removes the TH promoter methylation and DA over-production in the sub-cortical region which can lead to psychotic episodes. Although DA blockade may help to relief the psychotic episodes, it may worsen the negative or depressive symptoms. Indeed, a steady state level of the frontal lobe synaptic DA/NE is required to stabilize this condition and coordinately regulate the cognitive processing, mood and mental state.

With the exception of aripiperazole and clozapine which in addition to DRD2 blockage could increase the frontal cortex DA activities (13), other antipsychotic drugs as well as antidepressants were not able to stabilize such paradoxical conditions. However meta-analysis of 700 patients from 30 studies showed that concurrent use of L-dopa with antipsychotic drugs could further improve the symptoms of SCZ in half of the cases (71), non-specific increase in the DA production/level could not be a safe remedy in the long term. Similarly, MAO inhibitors were not suitable candidates to achieve these goals as they mostly inhibit DA degradation in the sub-cortical brain regions that may induce manic episodes. Nevertheless, as COMT is the main player for degradation of synaptic DA in the frontal lobe the potential roles of COMT inhibitors remain to be examined (31). However, recent reports indicating that even anti-psychotic and antidepressant drugs act through epigenetic mechanisms promises new insight in the treatment of psychiatric diseases (72).

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