Review Article

# Epigenetics in the nervous system: An overview of its essential role

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The role that epigenetic mechanisms play in phenomena such as cellular differentiation during embryonic development, X chromosome inactivation, and cancers is well-characterized. Epigenetic mechanisms have been implicated to be the mediators of several functions in the nervous system such as in neuronal-glial differentiation, adult neurogenesis, the modulation of neural behavior and neural plasticity, and also in higher brain functions like cognition and memory. Its particular role in explaining the importance of early life/social experiences on adult behavioral patterns has caught the attention of scientists and has spawned the exciting new field of behavioral epigenetics which may hold the key to explaining many complex behavioral paradigms. Epigenetic deregulation is known to be central in the etiology of several neuropsychiatric disorders which underscore the importance of understanding these mechanisms more thoroughly to elucidate novel and effective therapeutic approaches. In this review we present an overview of the findings which point to the essential role played by epigenetics in the vertebrate nervous system.

**Key words:** Behavior, cognition, development, environmental effect, epigenetics, maternal effect, neuropsychiatric disorders, plasticity, synaptic plasticity

## Introduction

'Epigenetics' refers to the study of mechanisms that cause specific and heritable changes in gene expression or cellular phenotype without alteration of the underlying deoxyribonucleic acid (DNA) sequence. They encompass functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence. Epigenetic mechanisms impose specific and heritable patterns of gene expression. The three key epigenetic mechanisms include: DNA methylation, histone modifications leading to nucleosome and chromatin remodeling and noncoding ribonucleic acid (RNA) mediated posttranslational regulation. The mechanisms of DNA methylation and histone modifications are well understood. Noncoding RNA molecules are a new class of molecules exhibiting epigenetic effects on gene regulation. Among the several types of noncoding RNAs, microRNAs have been reported to play roles in translational repression through either degradation of target messenger RNAs (mRNAs) or inhibition of mRNA translation.[1]

For a long time, scientists have sought to explain some fundamental questions regarding animal behavior and to verify if putative factors such as early life experiences, adversity, abuse, social interaction, etc., could explain adult behavioral patterns or if these patterns are essentially ingrained, immutable, and determined solely by our genetic makeup-the long standing "Nature versus Nurture" debate. The field of 'Behavioral Epigenetics' explores the relation between behavior and epigenetic alterations in specific brain areas and tries to interpret behavior in a broader context.[2] It is increasingly becoming apparent that epigenetic modifications play a vital role in nervous system development, function, and gene expression. Added to this we know that several functions in the nervous system such as neural development, adult neurogenesis, and modulation of synaptic plasticity

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requires stage specific gene expression for their proper progress.[3-5] Studies into the possible role of epigenetics in the nervous system have revealed that they play a pivotal role not only in the above mentioned process, but also in higher brain functions like learning and memory formation. These different roles will be the focus of this review.

## Neural Stem Cell Fate and Neurodevelopment

The initial cells that give rise to the central nervous system (CNS) arise from the neuroepithilial cells and neural stem cells (NSCs) which undergo a process called neurogenesis by which they form all the cell types found in the nervous system. An intricate network formed by extrinsic factors/molecules and the resulting cascade of transcription factors that are evoked as a result of signal transduction pathway together cause changes to the epigenetic state of the neural progenitors and influence their decision to differentiate along neural or glial lineages.

During early gestation, NSCs lack multipotency and undergo mainly asymmetric divisions to form neurons. During late gestation, they acquire multipotency and undergo asymmetric divisions to form astrocytes and oligodendrocytes.[6-8] Cytokine signaling by the interleukin-6 (IL-6) family cytokines are the chief extrinsic signals for turning on astrocytic differentiation.[9,10] Leukemia inhibiting factor (LIF) and ciliary neurotrophic factor (CNTF) are able to induce astrocyte cell fate via the Janus kinase (JAK) signal transduction activation of signal transducers and activators of transcription (STAT3) factor. The methylation status of the STAT3 binding site of the astrocyte marker called glial fibrillary acidic protein (GFAP) determines if an astocyte fate is induced or not. The hypomethylated state of the STAT3 binding site in the GFAP promoter at late gestation allows the activation of astrocytic genes.[11] Bone morphogenic protein (BMP-2), a member of the IL-6 family works by increasing histone acetylation at the promoter of S100β, another astrocyte marker during late gestation.[12]

Methyl-CpG binding domain (MBD) proteins are important in maintaining neuronal identity and differential plasticity.[13] They are abundantly expressed in neurons, but not in astrocytes and oligodendrocytes. Ectopic expression of MBD1 has been known to inhibit astrocyte differentiation while promoting neuronal differentiation in neuroepithelial cells which have become hypomethylated at the STAT3 binding site in the GFAP promoter, the reason being that they can still bind to DNA regions upstream of the STAT3 binding site and silence gene transcription by recruitment of repressor proteins.[13] Recently, long noncoding RNA (lncRNAs) has been shown to play a role in establishing and maintaining neural cell identity.[14]

What leads to the demethylation at the STAT3 binding site at late gestation?, The key epigenetic switch which turns on astrocyte development. Feng *et al*.,[15] observed the expression patterns of de novo DNA methyltransferases Dnmt-3a and -3b. They observed that they are differentially expressed in different types of CNS cells and their expression profiles indicated that they were dynamically regulated in the embryonic and adult CNS. They concluded that Dnmt-3a could possibly play a role in neuronal and astroglial differentiation based on its expression profile. Dnmt-1 (a maintenance methyltransferase) deficiency has been known to cause precocious astrogliogenesis.[16] Dnmt-3a and -3b also have maintenance functions.[17] Thus de-methylation may occur due to the downregulation of the maintenance methytransferases at late gestation. Apart from DNA methylation, histone modifications are involved in turning on astrocyte cell fate. Fibroblast growth factor-2 (FGF-2) and CNTF increase the accessibility of a complex formed by STAT3 and CREB (cAMP response element binding) binding protein (CBP) to the GFAP promoter by inducing H3K4 methylation and suppressing H3K9 methylation around the STAT3 binding site to induce astrogliogenesis.

Other transcriptional regulators nuclear receptor co-repressor (N-CoR) and orphan nuclear receptor TLX (tailless homolog) are responsible for promoting a neuronal cell fate by suppressing the GFAP gene. Knockout mutant lines for these genes showed precocious GFAP expression and increased differentiation to astrocytes respectively.[18,19] The role of basic Helix-Loop-Helix (bHLH) transcription factor Neurogenin1(Ngn1) which suppresses astrocyte cell fate even in the presence of CNTF and LIF was studied by Sun and colleagues.[20] They proposed a 'sequestration model' to explain the switch from neurogenesis to gliogenesis. Ngn1 sequesters an activator complex CBP/p300/Smad1 to the promoter of neuronal

fate inducing gene NeuroD. As gestation proceeds, Ngn1 is downregulated. STAT3 now complexes with Smad1 to initiate astrogliogenesis. The RE1 silencing transcription factor (REST/NRSF) complex also mediates neuronal gene expression.[21,22] When bound to the repressor element 1 or NRSE (RE-1/NRSE) site, transcription of neuronal genes is inhibited. Its dissociation from the site is sufficient to turn on some neuronal genes (Class I genes). An additional complex of corepressor CoREST and methyl DNA-binding protein (MeCP2) is involved in repression which binds to a site nearby the RE-1/NSRE site to repress transcription. It dissociates from this site in the event of membrane depolarization. When both inhibitory complexes are dissociated, a second class of neuronal genes (Class II) is expressed.[21] A review by Ballas[22] details the role played by the REST/NRSF complex in mediating neuronal gene expression.

## Neural Behavior

Early work by Meaney and Szyfon the effects of maternal care on the epigenome could precisely and elegantly confirm how early life experiences leave indelible epigenetic marks consequently determining behavior. Since then a number of studies carried out in similar vein have assessed the role of several putative factors known to influence behavior. Epigenetic effects have been explained well in the case of mouse models, but the lack of clear-cut evidence in humans makes it difficult to ascertain the role played by them in the human context.[23-25]

Early life experiences and stressful events can have long-lasting effects on brain development and the capacity of an individual to respond to stress later on in life.[26] This happens by the alteration of neuroendocrine responses, metabolic and immune system function.[25] During sensitive stages, especially in early development, stimuli are transmitted to the brain and influence functions of neurons and key neural pathways which determine behavior in later life.[26] The quality of the prenatal and early postnatal environment are important phases where some of the basis for adult behavior could be hard wired including vulnerability to stress, susceptibility to disease, cognitive deficits, etc.[27,28]

The following table lists some of the known effects of early-life experiences and environmental factors which have been shown to have an epigenetic cause [Table 1].

### *Epigenetics in neural plasticity, memory, and learning*

Long-term changes in synaptic plasticity in the fundamental basis for learning and memory. In Aplysia, histone acetylation and deacetylation dynamics modulates the turning on or off of the memory-related genes. CBP which has histone acetyltransferase (HAT) activity is important for long-term memory particularly in the context of contextual fear conditioning and novel object recognition.[40-42] An excitatory neurotransmitter induced the expression of CREB binding protein (CBP1/CBP) leading to the activation of CCAAT-enhancer binding proteins (C/EBP) required for long-term facilitation (LTF). Inhibition of C/EBP can occur leading to long-term depression by the histone deacetylase (HDAC) repressor complex containing activating transcription factor 4 and HDAC (ATF4/HDAC5) on the target gene promoter.[43] In mammalian models of synaptic plasticity N-methyl-D-aspartate (NMDA) receptors and mitogen activated protein kinase/ extracellular signal-regulated kinase (MEK-ERK/MAPK) signalling have been implicated to increase histone acetylation (H3) especially in contextual fear conditioning.[44-46] SWItch/ sucrose non-fermentable family of chromatin remodeling proteins associate with HATs or HDACs and other transcription factors to activate and repress target memory related genes.[47] Poly ADP-ribosylation carried out by polyADP-ribose polymerase-1 is need for long-term memory.[48] Brain-derived neurotrophic factor (BDNF) is a key regulator of synaptic plasticity and memory formation.[49] Bredy *et al.*,[50] observed histone modifications around specific bdnf promoters which correlated with memory formation. During the consolidation of fear memories differential methylation is observed in the bdnf promoter which is dynamically regulated.[51] Detailed reviews have dealt with the important role played by epigenetics and the bdnf gene in synaptic plasticity, learning, and memory formation.[49,52,53]

Recently, Moutri and colleagues at the Salk Institute at La Jolla, California observed a surge of long interspersed nuclear elements (LINE) which are normally inhibited in NSCs (through chromatin condensation and Sox 2/HDAC1 repression).[54-56] They proposed that these elements which

**Table 1: Early-life experiences/environmental factors and their associated epigenetic modification**

| Early life event/specific experience | Adult behavior that was affected | Region/gene where the epigenetic modification was observed | Possible connection | Additional remarks | Reference |
|---|---|---|---|---|---|
| Maternal effect: Pup licking and grooming (LG) and arched-back nursing (ABN) | Stress response (moderate to high hypothalamic-pituitary-adrenal (HPA) response) and fearfulness | Exon 17 (non-coding) region of GR gene. Modifications: Deoxyribonucleic acid (DNA) methylation, histone acetylation | De-methylation at NGFI-A binding site allows to increased GR expression and moderate HPA stress response | DNA methylation patterns Emerged in the first week of life Reversed by cross-fostering Reversal by histone deacetylase (HDAC) inhibitor trichostatin A (TSA) | 23,24,25 |
| Maternal effect: LG | Maternal care behavior of female rats mediated by oxytocin responsiveness | Estrogen receptor (ER)-α gene expression in medial preoptic area (MPOA) of hippocampus Modification: DNA methylation | Female offspring of low LG mothers have high levels of ERα promoter methylation hence low oxytocin responsiveness | Clearly shows epigenetic perpetuation of behavior across generations | 29,30 |
| Maternal deprivation (MD) | Hippocampus-dependent memory tasks such as reflex development | Reelin gene Modification: DNA methylation | Increased DNA methylation decreased reelin expression in the hippocampus | Neurobehavioral changes were linked to reelin expression in hippocampus | 31 |
| Early-life abuse | Neural mechanisms of cognition and emotion | BDNF gene expression in prefrontal cortex (PFC). Modification: DNA hypermethylation in the regulatory region of BDNF gene | Decreased BDNF expression in PFC leads to cognitive deficits and aberrant emotional behavior | Altered methylation pattern was found to be transmitted to offspring of females exposed to abuse Rescue through HDAC inhibitor Zebularin | 32 |
| Early-life abuse | Predisposition to suicidal behavior | Glucocorticoid receptor (GR) promoter Modification: DNA hypermethylation | Decreased GR expression linked to suicidal tendencies | Observed in post mortem brains | 33 |
| Social defeat/ bullying by bigger mouse | Depression-like behavior | BDNF gene Modification: Histone modification | Histone methylation at BDNF promoters led to suppressed BDNF gene activity in the hippocampus | Anti-depressant Ipimarine administration reversed depressive traits by downregulation of HDAC 5 | 34 |
| Social conflict model | Social stress | Inflalimbic medial prefrontal cortex (mPFC) Modification: H3 acetylation and H3 phosphoacetylation | Plausible link between stress induced chromatin remodeling and increased ΔFosB expression | ΔFosB immunoreactive cells were increased in mPFC | 35 |
| Mouse strains of differential stress response | Susceptibility to stress and depression | GDNF promoter in NAc Modification: DNA methylation, histone modifications | Epigenetic regulation of GDNF promoter in the NAc | | 36 |

**Other neurobehavioral phenomenon with known epigenetic links**

| Observed phenomenon | Epigenetic link | Additional remarks | Reference |
|---|---|---|---|
| Cognitive deficits and hyper-anxiety like behaviors | KAP1 mediated epigenetic repression; Genes Mkrn3 and Cdkn1c Modification: H3K9 trimethylation, H3 and H4 acetylation | KAP1 knockouts show overexpression of genes that induce anxiety | 37 |
| Age associated memory impairment in rats | Hippocampus Modification: H4K12 acetylation | Deregulation of H4K12 acetylation leads to failure to initiate hippocampal gene expression program | 38 |
| Posttraumatic stress disorder | Altered DNA methylation profiles | Occurs possibly through low levels of DNA methylation in immune related genes | 39 |

can insert new copies of themselves into other areas of the genome could have deeper functional consequences than was previously understood. Epigenetics and retrotransposition may confer properties such as somatic variability, plasticity, and the required complexity to the cells of the CNS to carry out their complex tasks.

## Structural Plasticity: The Adult Neurogenesis Paradigm

Adult neurogenesis occurs in two principal areas in the brain namely the subgranular zone of the hippocampus dentate gyrus and the subventricular zone. In a review

by Hsieh and Eisch,[4] a detailed view of hippocampal neurogenesis and its implications in neuropsychiatric disorders has been discussed. The impediments in understanding the neurogenesis puzzle are associated with the difficulty in tracking adult-generated neurons *in vivo*, isolating NSCs and the association of several signals arising from niche cells such as astrocytes, nearby neurons, and endothelial cells.[57] However much has been learnt about the intrinsic epigenetic mechanisms involved in the process.

Ma *et al*., investigated activity-dependent neurogenesis in the adult hippocampus; one of the main types of neural plasticity exhibited by the mammalian brain.[58] They discovered the interesting role played by growth arrest and DNA-damage-inducible protein beta (Gadd45) in active DNA demethylation of specific promoters of genes required for adult neurogenesis. Mature dentate gyrus neurons were activated by electroconvulsive therapy (ECT) which saw a concomitant increase in hippocampal neurogenesis. Gadd45b which belongs to a family of proteins implicated in DNA repair[59,60] was strongly induced by ECT. Gadd45b knockouts showed less effective ECT induced neurogenesis and also attenuated dendritic growth of newborn neurons compared to their wildtype counterparts. Significant demethylation was found at regulatory regions of the bdnf and FGF-1 genes which promote dendritic growth and neural progenitor proliferation, respectively.[58] Chromatin immunoprecipitation (ChIP) assays confirmed the binding of Gadd45b to the regulatory regions of these genes confirming its role in effecting locus specific DNA demethylation in the mammalian system. The same author followed-up this discovery with a review titled 'Epigenetic choreographers of neurogenesis in the adult mammalian brain',[61] which dealt with intrinsic epigenetic mechanisms and extrinsic niche signaling involved in adult neurogenisis.

## Epigenetic Dysregulation is Associated with Many Neuropsychiatric Disorders

As a consequence of the important role played by epigenetics in a number of processes in the nervous system, it is hardly surprising that the deregulation of epigenetic mechanisms has been implicated in a number of neuronal diseases.

Table 2 lists epigenetic links to certain neuropsychiatric disorders, drug addiction, and effect of substance use during pregnancy.

### *Conclusions and future perspectives*

The studies presented above indicate that intrinsic epigenetic mechanisms play a crucial role in several processes occurring in the nervous system from NCS differentiation to complex tasks like learning and memory formation. The dynamic nature of epigenetic modifications have made them ideal for carrying out many of these functions which rely on precise spatial and timely orchestration of gene expression patterns. The large repertoire of modifications that can be performed on the histone tails and the addition and removal of methylation marks on cytosines make it possible to carry out many of these functions. With new types of modifications being discovered like the recent discovery of hydroxymethylcytosine and the implication of DNA repair enzymes in de novo demethylation, we are beginning to understand the scale of the molecules that are involved in these processes. Epigenetic mechanisms have in essence been co-opted by the nervous system to perform several of the complex tasks that it performs and as such it explains elegantly how many of these functions are carried out at the molecular level. Its particular success in explaining the effect of early life experiences, maltreatment, and social stress in animal models of behavior has garnered much attention and very soon we may have answers of how exactly they operate in the human context. So it seems that some of society's complex problems could be explained by simple molecular mechanisms occurring at the cellular level and also opens the doors for possible therapeutic interventions at the proper times to counteract the effects of abuse or neglect. Diseases with an epigenetic basis for their pathology are being investigated to device more directed approaches towards treating these ailments. Overall, the understanding of the role of epigenetics in the nervous system has opened doors for investigation in a plethora of subfields and promises to provide answers some of the deepest questions concerning the human brain and also cures for many neuropsychiatric diseases.

**Table 2: Epigenetics in neuropsychiatric disorders**

| Neuropsychiatric disease | Epigenetic link | Reference |
|---|---|---|
| Rett's syndrome | MeCP2 mutation | 62, 63 |
| Rubinstein-Taybi syndrome | Heterozygous mutation in CREB (cAMP response element binding) binding protein (CBP) | 62, 64 |
| Fragile X syndrome | Hypermethylation of deoxyribonucleic acid (DNA) at the FMR1 and FMR2 promoters, caused by trinucleotide repeat expansion | 62, 65 |
| Immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome | Mutations in Dnmt3B; hypomethylation at centromeric regions of chromosomes 1, 9, and 16 | 62, 66 |
| Coffin-Lowry syndrome | Mutation in RSK2, which can interact with CREB and CBP and can phosphorylate H3 *in vitro* 106 | 66,67 |
| Prader-Willi syndrome | Abnormal imprinting (DNA methylation) of paternal chromosomal region 15q11-13 | 68,69 |
| Anglemann's syndrome | Abnormal imprinting (DNA methylation) of maternal chromosomal region 15q11-13 | 68,69 |
| Depression | Epigenetic deregulation leads to reduced neurogenesis and impaired neuronal plasticity; main factors in the pathogenesis of depression, behavioral despair, and cognitive deficits | 70 |
| Pediatric and adult nervous system tumors | Epigenetic alterations implicated in tumor maintenance and progression | 71 |
| Schizophrenia | Epigenetic repression of Reelin and glutamic acid decarboxylase 1 or GAD67 | 72 |
| Epilepsy | Through epigenetic deregulation of synaptic plasticity and neurogliogenesis | 73,74 |
| **Epigenetics in drug addiction and compulsive drug-seeking behaviors** | | |
| **Drug** | **Epigenetic modification** | **Reference** |
| Chronic cocaine administration | Two genes silent mating type information regulation homologs 1 and 2 (SIRT1 and SIRT2) were hyperacetylated at H3 in NAc | 75 |
| | H4 hyperacetylation was seen at the cFos gene promoter and H3 hyperacetylation in BDNF and cyclin dependent kinase (CDK5) gene promoters in the striatum | 76 |
| **Epigenetic changes in offspring occurring due to the quality of prenatal environment** | | |
| **Environmental effect** | **Epigenetic modification** | **Reference** |
| Consumption of alcohol during pregnancy | Unknown | 77 |
| High levels of depression and anxiety during the third trimester | Increased methylation of GR promoter (as observed in cord blood cells) | 78 |
| Exposure to cocaine during second and third trimesters of gestation | Global changes in DNA methylation in the hippocampus | 79 |

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