Epigenetics, Mental Health and Transgenerational Epigenetic Effects

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Abstract

Objective: to review the field of epigenetics, and present basic and recent material that may be of interest to clinical psychiatrists. We include basic molecular mechanism, a consideration of findings related to mental disorders, evidence of sustained effects, and the evidence for and implications of transgenerational epigenetic modifications. Method: we examined all the available papers for the last five years identified by PubMed using the words ‘epigenetics’ and ‘epigenetics psychiatry’, and the available leading specialized textbooks. Results: we report on molecular mechanisms including DNA and histone modifications, and non-coding RNAs. While some modifications are short-lived, others are life-long. Depression, suicide, schizophrenia, PTSD, borderline personality disorder and drug addiction are among the conditions for which epigenetic involvement has been proposed. Transgenerational epigenetics enables the environmental experience of one generation to be non-genetically inherited by subsequent generations. This has been molecularly demonstrated in laboratory animals and epidemiologically suggested in humans. Conclusions: epigenetics provides a new way of understanding human behavior and points to potential therapies for mental disorders. Should it transpire that transgenerational epigenetic modifications apply with force in humans as they do to laboratory animals, this will emphasize the need for cultural shift, safe societies with ample opportunities.

Keywords: Mental Disorders, Psychiatry, Epigenetics, Health, Histone, DNA Acetylation

Introduction

For decades we believed that nature (genetic endowment) and nurture (environment) determined our phenotype (physical and behavioral assets and diseases) and there were no other significant influences. Recently we have learned of a new level of influence, the epigenome, which provides a molecular explanation of the nature-nurture interaction, and allows a mechanism for altering the phenotype, not only in the young, but throughout life¹.

Epigenetics is an emerging field which will impact on our understanding of mental
health. While the definition has been debated at an esoteric level\textsuperscript{2,3}, the following is adequate for our purposes: “The study of mitotically and/or meiotically heritable changes in gene formation that cannot be explained by changes in DNA sequence”\textsuperscript{4}. Thus epigenetic modification may explain how environmental features effect life-long changes in phenotype of the individual and even transgenerational gene expression in offspring.

Adverse conditions during early life are a risk factor for stress related diseases such as depression and post-traumatic stress disorder\textsuperscript{5}. Such studies suggests epigenetic factors may have a role to play in these and other mental disorders.

**Molecular Mechanisms**

**Chromatin**

Chromatin is the combination of DNA and proteins which are contained in the nucleus. The DNA is coiled around histone proteins. The basic unit of chromatin is the nucleosome, which is composed of about 147 base pairs of DNA wrapped around (about 1.65 turns) a core histones (two copies of four different histones)\textsuperscript{6}. Each histone has an amino-terminal ‘tail’ composed of amino acid residues.

In simple terms, chromatin exists in two basic states. In ‘condensed’ chromatin (heterochromatin), the DNA and histone cores are tightly packed, transcription is not possible and the gene is inactive or ‘silenced’. In ‘relaxed’ chromatin (euchromatin) transcription is possible and the gene is termed ‘active’.

**DNA modification**

One epigenetic adaptation which regulates (usually suppressing) gene expression is the addition of methyl groups to DNA. These come from S-adenosyl methionine (SAM) and are transferred to cytosine residues where the cytosine nucleotide occurs next to a guanine nucleotide (CpG). The cytosine is thereby converted from cytosine to 5-methylyxocine. This process is catalyzed by DNA methyltransferases (DNMTs)\textsuperscript{7}.

High concentrations of CpG sequences occur in ‘promoter regions’ - segments of DNA where DNA transcription complexes bind when they begin copying the DNA to make RNA.

**Histone modification**

Each histone has an amino (N) terminal tail. Acetylation of tails causes the relaxation chromatin, and allows active gene transcription. The catalyst is histone acetyltransferases (HATs), and is reversed by histone deacetylases (HDACs)\textsuperscript{8}. In contrast to acetylation, histone methylation can cause either with gene activation or repression, depending on the residue being methylated. For example, methylation of histone H3 at Lys9 is associated with gene silencing\textsuperscript{9}.

Modifications can also be accomplished by a range of other processes, including phosphorylation, ubiquitylation and SUMOylation\textsuperscript{7}.

**Non-coding RNAs**

Non-coding (nc)RNAs are a new source of influence over gene regulation\textsuperscript{10}. A classification includes ‘small’, 20-200 nucleotides (nt) and ‘long’ ncRNAs, greater than 200 nt. For a detailed review see Spadaro and Bredy\textsuperscript{11}. Small ncRNAs include micro (mi), short interfering (si), and P-element induced wimpy testis (PIWI)-interacting (Pi)RNAs\textsuperscript{12}. MicroRNAs are endogenous and mediate gene silencing by binding to their target mRNA. Around 200 miRNAs have been identified to the present
time, and more than 33% of the mammalian genome is subject to miRNA regulation.

Further mechanism
Epigenetics is an emerging field; further mechanisms will be identified. The influence of the immune system on epigenetic processes will provide valuable information.

Long-Term Phenotype
Epigenetics provides and explanation for the mystery of how cells of multicellular organisms (including humans) are genetically homogeneous but may be structurally and functionally different (liver and brain cells, for example).

Human cardiovascular disease has origins in early life but may not become apparent till later in life, and the likely mediator is epigenetic dysregulation of gene expression.

While epigenetic changes may only persist for short periods, others, as in the differentiation mentioned in the first paragraphs, may persist across the lifespan. Many animal studies demonstrate the lasting effects of early life experiences. Good rat mothering of pups includes high level of licking, grooming and arched back nursing (high LG-ABN); naturally, some mothers demonstrate low LG-ABN. When the pups of low LG-ABN mother are switched to a high LG-ABN, and subsequently have their own litters, their offspring demonstrate high LG-ABN. The offspring of high LG-ABN mothers, compared to offspring of Low LG-ABN mothers, are less anxious, have attenuated corticosterone responses to stress and increased expression of glucocorticoid receptor mRNA and protein in the hippocampus.

It is not only the newborn that are subject to environmental influence. Mammalian studies have demonstrated experience dependent epigenetic modifications in adults which may have long-lasting effects within mature neurons.

As is widely accepted, children who are neglected or maltreated are at risk of developing lasting emotional and behavioral problems. The major mechanism is DNA methylation, which predisposes these individuals to stress-related problems in later life.

Specific Mental Health Disorders
Mood Disorders
Chronic social defeat stress in mice (a model of depression) is associated with chromatin remodeling by increased histone methylation at the promoter regions of BDNF genes in the hippocampus. Imipramine treatment reversed this process by histone acetylation at the promoters. Thus, in the sub-primate mammals, histone remodeling appears to have been implicated in the pathophysiology and treatment of depression.

This is consistent with human studies which have demonstrated low levels of BDNF in depressed compared to healthy individuals, which in turn are raised by antidepressant treatment. The treatment of depression with citalopram decreases histone methylation levels at the BDNF gene. Subsequent increases BDNF levels are related to the antidepressant response.

At the clinical level, features of depression including the gradual onset and slow response to treatment, suggest slowly developing but stable adaptations, which is consistent with epigenetic regulation.
In bipolar disorder, a study of monozygotic twins discordant for the disorder, demonstrated a role for DNA methylation differences in mediating the phenotypic difference. A GABAergic system dysfunction has been proposed in bipolar disorder. This is supported by the finding of GABAergic gene expression downregulation which was demonstrated in postmortem brains of people who had suffered bipolar disorder.

**Suicide**
Suicide is not always the result of mental disorder, however, this does not exclude biological explanations, and such explanations can be reasonably expected to be similar to the findings in mood disorders.

One study examined the epigenetic differences in a glucocorticoid receptor (NR3C1) promoter in the postmortem hippocampus of people who completed suicide; those with a history of childhood abuse were compared with those without. Changes suggested an effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor (GR) expression; those who had been abused children displayed low GR levels and elevated DNA methylation of the GR promoter.

Low levels of BDNF have been reported in suicide. A postmortem study of the Wernicke area of suicide subjects found hypermethylation of the BDNF promoter, which could explain the downregulation of BDNF expressed in this population.

In a recent genome-wide investigation of the brains of suicide subjects, broad reprogramming of promoter DNA methylation patterns in the hippocampus were demonstrated. At this stage, the definitive modifications related to suicide have not been identified.

**Schizophrenia**
Both genetic and environmental factors are involved in the etiology of schizophrenia. While the liability to schizophrenia is strongly heritable, however, about 90% of those who develop this disorder do not have a parent with this disorder. Therefore, environmental factors are important in the etiology of this disorder.

Some work has highlighted epigenetic alterations at the reelin promoter. Reelin is a glycoprotein found in adult GABA-containing neurons. Postmortem studies of people who suffered schizophrenia have demonstrated down-regulation of reelin expression is several parts of the brain. This could cause dysfunction of GABA system.

Also consistent with the GABAergic pathology theory of psychosis, evidence for aberrant epigenetic regulation of GABAergic signaling was found in postmortem prefrontal cortex of people with a history of schizophrenia. Clozapine, olanzapine and quetiapine were shown to facilitate chromatin remodeling, while haloperidol and risperidone are inactive in this respect.

A genome-wide study of peripheral blood of monozygotic twins discordant for schizophrenia has reported differences in DNA methylation, which may help to explain the different phenotypes.

**Unwanted fear and PTSD**
Long-term memory formation is achieved via selective changes in gene expression. Unwanted fear and post-traumatic stress disorder (PTSD) appear to be underpinned by epigenetic changes secondary to the obvious stressor. In the rat, fear learning is associated with altered DNA methylation.
and histone modification at the BDNF gene locus in the hippocampus of adults. Rodent models of PTSD are used in early therapeutic investigations. In one rat study, garcinol, a naturally occurring histone acetyltransferase (HAT) has been shown to disrupt the consolidation and reconsolidation of Pavlovian fear conditioning. Garcinol was administered both systemically and by injection into the lateral amygdala. Both disrupted consolidation and reconsolidation of unwanted memories, which was associated with acetylation of histone H3 in the lateral amygdala. The authors suggest that the use of a HAT inhibitor in combination with psychotherapy may have therapeutic potential.

**Borderline personality disorder**

One of the established etiological factors of borderline personality disorder (BPT) is adverse childhood experiences. Down-regulation of BDNF gene expression associated with methylation at promotor sites has been described in BPD. In a study of people with BPD the percentage of methylation at two BDNF gene CpG sites was determined. BPD people had significantly higher methylation at both sites, compared to controls, and the severity of abuse was proportional to the degree of methylation. Psychotherapy was then provided, and those who had a clinical response showed a decreased methylation status. These results support the theory that BPD is associated epigenetic interference with the BDNF gene and that this abnormality may be corrected by appropriate treatment.

**Alzheimer’s disease**

The possibility that epigenetic mechanisms play a role in etiology of Alzheimer’s disease has supported. In mouse memory impairment (model of Alzheimer’s disease) enhancing histone acetylation using HDACs can ‘rescue’ memory deficits. This approach may have utility in the treatment of Alzheimer’s disease.

**Drug and alcohol addiction**

Drugs of abuse exert control over addicted users by commandeering the brain reward centers. Changes have been demonstrated in the mRNA levels in the ventral tegmental area, nucleus accumbens, hippocampus and other brain centers which may be long-lasting. Chronic alcohol use leads to histone modifications and DNA methylation in the amygdala. Stimulant addiction is associated with histone modification, DNA methylation and miRNAs may all contribute to altered BDNF expression.

While epigenetic modifications have been identified in drug addiction, discussion continues as to whether/which of these are predisposing factors and which are responses to drug use.

**Other psychiatric disorders**

It is probable that epigenetic modifications will be important in other psychiatric disorders. Eating disorders and stress responsiveness and anxiety have received recent some attention.

**Transgenerational Epigenetic Modification**

The possibility that the phenotype of offspring being influenced by the environmental experience of his/her parents is of profound importance in mental health. It may mean that adverse early life experience and the war (or similar) experience of adults could have damaging effects on subsequent generations, further emphasizing the responsibility of society to provide for the disadvantaged and prevent war and other trauma.
Epidemiological studies demonstrate that environmental factors can, in the absence of DNA sequence changes, result in particular phenotypes in subsequent generations. When food is not readily available during the period prior to the growth spurt of men, cardiovascular disease mortality is reduced in the next generation. Alternatively, if food is plentiful at this stage, diabetes mortality is increased in grandchildren. Other reports come from the Dutch Hunger Winter; mothers who were malnourished during the first trimester gave birth to babies of normal weight, but their babies (next generation) tended to be heavier than normal. This pattern strongly suggests transgenerational epigenetic effects.

The epigenetic modifications are generally cleared on passage through the germ-line. However, some remain allowing some phenotypes to cross into the next generation. In mice the inheritance of epigenetic modifications at the agouti locus of dams results in variation in coat color. These authors speculate, ‘this type of inheritance may be common’. In another mouse study, epigenetic modifications resulting in ‘kinked tail’ was inherited via either maternal or paternal transmission. Also, in Drosophila (fruit fly), environmental stress induces chromatin disruption which is inherited over several generations.

Histone modification and ncRNAs are suggested as the main mechanisms of non-genetic inheritance that persists for multiple generations. DNA methylation may also play a role.

The epigenetic transgenerational effects of chemical toxins have been studied. One rat study demonstrated that gestating females exposed to an industrial fungicide passed on sperm epigenetic alterations leading to adult onset male testis disease. Another, in which gestating females were exposed to hydrocarbons (jet fuel), showed the 3rd generation manifested ovarian disease, obesity and other pathologies.

Rat mothering of pups (high and low LG-ABN) has been mentioned above. The offspring of low LG-ABN mothers who are raised by high LG-ABN mothers, become high LG-ABN mothers and this phenotype transmitted across generations.

A mouse study revealed that postnatal stress of parents leads to depressive-like behaviors, impaired social interactions and increased risky and reckless behavior in offspring, which is then inherited across at least two generations. A review found that stressed rodents became anxious and this unwanted condition could be passed to subsequent generations.

A rat study reported that when mothers/caretakers were experimentally stressed, they maltreated the young in their care. This led to altered BDNF gene expression in the young, and after growth, altered gene expression in the adult prefrontal cortex. Important, transgenerational epigenetic modifications were passed on to subsequent generations. Elevated methylation in the BDNF gene was observed to be inherited by 3rd generation rats born to abused pups.

There are numerous examples of the administration of stimulants and narcotic to rodents resulting in altered behavior in offspring. In mice, paternal cocaine administration results in impaired working memory in female offspring. Again in mice, exposure of mothers to cocaine results in abnormal DNA methylation in the hippocampus of male offspring for up to 30 days of life.
Rat sires allowed unrestricted self-administration of cocaine produced male (but not female) offspring who had reduced tendency to use (decreased reinforcement) cocaine (a finding which runs counter to what is supposed to occur in humans). The proposed mechanism is BDNF promoter acetylation resulted in medial prefrontal cortex.

**Discussion**

A limitation of this paper is that it was written by clinical psychiatrists with modest training in genetics and epigenetics. This need not be a fatal flaw, however, as we are writing for fellow clinical psychiatrists, and we have taken care to accurately present simplified material.

Epigenetics is a revolution in understanding; it adds an ‘extra layer’ to the nature-nurture debate, and promises to throw open the doors to new theory and eventually, improved clinical practice.

Authorities have already suggested the use of enzymes involved in epigenetic mechanism (such as HATs, HDACs and DNMTs) in therapy for alcohol problems. There is also the suggestion that HATs (which increase acetylation) may have a role in the therapy of unwanted fear and PTSD, while HDACs (which decrease acetylation) may be explored as therapy for Alzheimer’s disease.

It is early days, and knowledge is incomplete. For example, with respect to drug addiction, epigenetic modifications have been demonstrated, but it is not yet clear whether these are predisposing or a response factors.

We have used human epidemiological studies to cardiovascular disease to the demonstrate the impact of environmental factors on health. We have highlighted the evidence for epigenetic modification leading to physical disease in rats, and many rodent models of mental disorders and outlined some recent human epigenetic discoveries.

Of enormous interest is that epigenetics gives a molecular explanation for long recognized behavioral responses to childhood adverse events and drug addiction. Also, there is the promise of better understanding other major mental problems including schizophrenia, mood disorder, mood disorder, and borderline personality disorder. The BDNF gene promoter has been suggested as an area of interest in mood disorder, suicide, PTSD, drug addiction, and borderline personality disorder, as well as laboratory animal studies.

We have provided convincing evidence of mammalian transgenerational epigenetic alterations. Epidemiological studies of human nutrition and health suggest transgenerational epigenetic modification.

Of enormous concern is the possibility that transgenerational epigenetic modifications may be common in humans. Should we discover that an adverse environment of child or the adult experience can lead to non-genetically inherited maladaptations or diseases in subsequent generations, humane, social, public health and economic issues will soar. This will call for a redoubling of our efforts to provide a safe world in which all receive ample opportunities.

**Conflicts of interest:** none.
References


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