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Epigenetics and Depression: A Rabbit Hole of Discovery

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Abstract

"After this, there is no turning back. You take the blue pill—the story ends, you wake up in your bed and believe whatever you want to believe. You take the red pill—you stay in Wonderland, and I show you how deep the rabbit hole goes. Remember: all I'm offering is the truth." Epigenetics is a bit like the red pill—the more it is researched the further down the rabbit hole we are going—the realisation that my choices today as my parents' and grandparents' choices yesterday influence who I am now and who I am going to be tomorrow. Through the study of gene influencers, scientists are discovering that it is not only the DNA that makes us but which portion of is selected for use that tells us who we are. In the field of depression, epigenetics is still in its infancy, nonetheless significant connections have been uncovered. This paper gives a brief overview on epigenetics and the different mechanisms correlated with it. It also discusses factors affecting an individual's epigenetic patterns and the effect of epigenetics itself. It specifically delves into the epigenetic effects on psychiatry, mainly depression, depressive symptoms and antidepressant treatments and the mediation of mechanism of action of the epigenetic modifications involved.

Keywords

Epigenetics, Depression, DNA Methylation, Histone Remodelling, Inheritance, Environment

1. What Is Epigenetics?

1.1. A Basic Overview

Not everything that is inherited is genetic. Along with the genes, chemical markers found on the genes undergo duplication when DNA is replicated [1].

Epigenetics is the variations in gene expression which aren't a result of DNA

sequence modification. It is mainly characterised by histone tail modification or DNA methylation. In general, this means that "tags" or "tails" are added to the DNA in order to switch on or switch off certain genes (in the case of methylation) and to enhance or diminish activity of certain genes (in the case of histone modification). The epigenetic changes can be inheritable or environmental in nature and refer to changes which are in themselves reversible in nature. The epigenetic effects may give rise to phenotypical differentiated cells and tissues within an organism [2] [3].

Epigenetics is a cornerstone in evolution and aids in determining the success of a species. A prosperous population is one that can juggle a consistency in phenotype when presented with a stable surrounding environment and an ability to change phenotype as a reaction to a drastic environmental shift. Phenotypical changes can dually result: directly, from a change in the genome itself by steady physical changes in DNA sequence which would ultimately lead to mutations; and indirectly, as reversible chemical alterations in nucleotides or chromatin structure ultimately leading to epi-mutations [4].

Epigenetics is a wide term that mainly encompasses inherited and environmental factors which give rise to the various mechanisms of DNA expression regulation [5].

1.2. Chromatin, Histones and Remodelling

Proper functionality of a eukaryotic cell requires the compression of the long DNA strand into a minute nucleus. A 2-metre-long strand has to squeeze into a 5-micrometre space and in doing so the strand still has to be adequately accessible and unwindable to allow for replication, transcription and DNA repair—necessary functions for development and tissue-specific roles. Histones bring about the compression of chromatin. DNA is negatively charged and histones are positively charged, the opposing charges create a strong adherence of DNA to histone octamer in the formation of nucleosomes. In between each nucleosome H1 prompts further compacting into a chromatin fibre. Further coiling would result in euchromatin and then heterochromatin. This is seen depicted in the following diagram (**Figure 1**) [6] [7].

Modifications of DNA alter its structure. This is done by the changing of physical properties of individual nucleosomes chiefly through the addition or removal of charges from or to the target proteins or nucleic acids. The communication between charge of residues and the structure of chromatin is more often than not indirect. The state of chromatin in most scenarios depends on the complex interactions of the alterations of the vast amount of specialised nuclear proteins.

The structure of the chromatin is controlled and differentiated by a variety of processes:

- DNA methylation—nucleotide covalent alteration in which a methyl group is either added to a cytosine residue at position C-5 or N-4, or to an adenine

residue at position N-6 [8].

- ATP-dependent remodelling of nucleosome cores—utilising the energy from ATP hydrolysis to form, disturb or relocate nucleosomes by altering Histone—DNA interactions [9].
- Covalent modifications of histone tails—histone acetyltransferase, HAT, and histone deacetylase, HDAC, complexes, activate and repress transcription of genes respectively by determining the level of acetylation of the amino-terminal domains of nucleosomal histones associated with them [10].
- Replacement of core histones by their alternatives—histones synthesis occurs mainly at S phase for swift deposition after replication forks to fill in openings resulting from the dispersal of pre-existing histones. In addition, the replacement of established S-phase histones by variants, independent of replication, can possibly differentiate chromatin. "The replacement of a canonical histone by a non-canonical variant is a dynamic process that changes the composition of chromatin." [11]
- Nucleosome eviction—exposes associated DNA through ATP-dependent remodelling, specifically a change in the location or composition of nucleosomes in relation to the DNA that is wrapped around it [6].

Figure 2 portrays the mechanisms of chromatin structure variation.

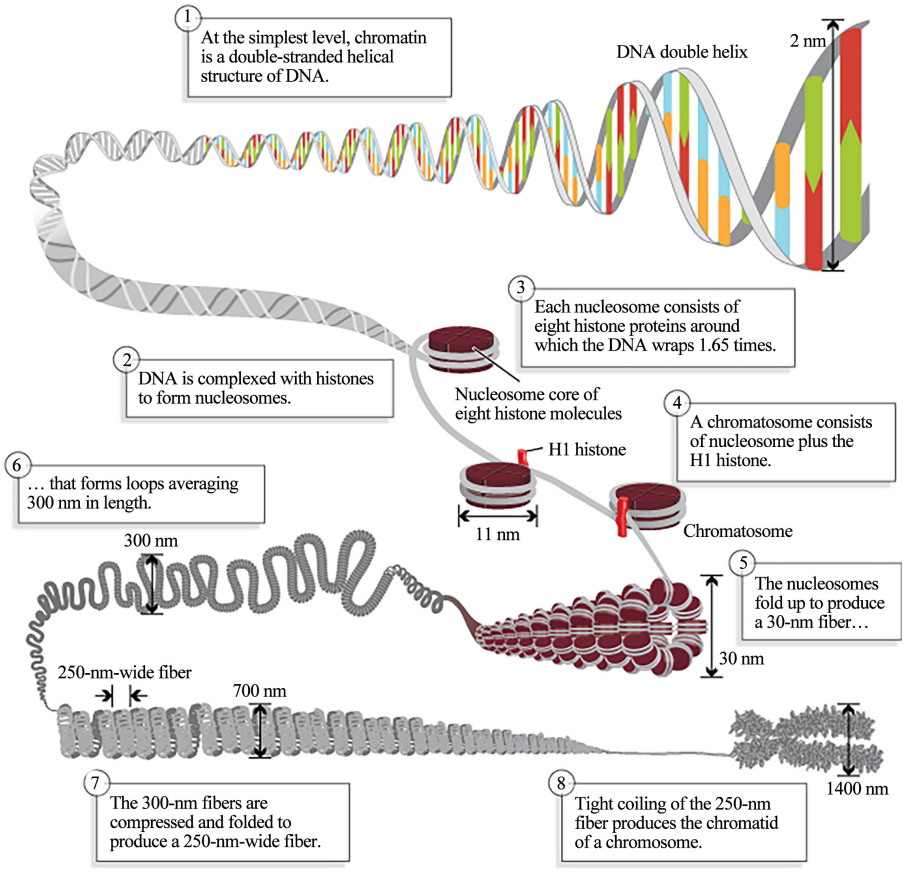


Figure 1. The role of histones in DNA Packaging [7].

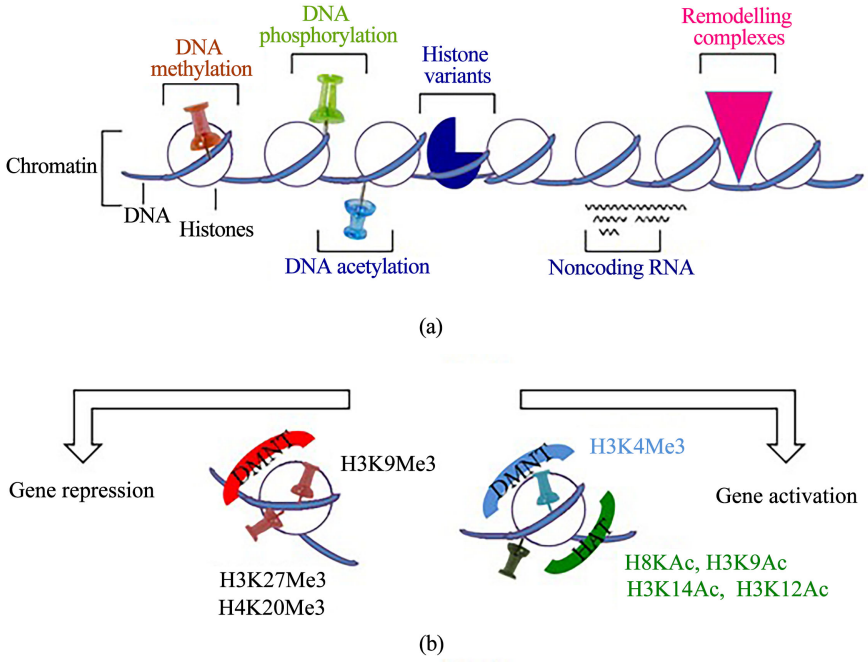


Figure 2. Epigenetic Modifications, repression and activation [12].

1.2.1. DNA Methylation

DNA methylation is one of the oldest mechanisms of gene expression regulation. Specifically, the addition or removal (demethylation) of a methyl group affects regulation, and the timing and specific sequence area targeted determine the timing and occurrence of cellular events.

A gene is not allowed to transcribe *i.e.* rendered useless by blocking off the start site or near the start site of transcription of that particular gene. The start site or promoter region is marked by a cytosine followed immediately by a guanine reading in the 5' → 3' direction. They are separated only by a phosphate and therefore the site is aptly referred to as a CpG site—cytosine, phosphate, guanine [3].

Methylation occurs symmetrically at the CpG site, meaning that both DNA strands carry the marker. GC (guanine—cytosine) content in the human genome is around 42%, therefore, if the numbers were to follow the ratios seen in other animal models CpG sites would be at 4.41%. However, they are represented at a frequency of less than 1%. Conversely, the CpG sites are more commonly found in clusters referred to as CpG islands which are constituted by 50% of GC with an observed is to expected occurrence of CpG higher than 0.6 in the length of 200 nt (nucleotides). Even though, only about 10% of all the cytosines in a genome are methylated, CpG islands play a crucial in transcriptional silencing [8] [13] [14].

DNA methylation patterns are brought about by:

- A family of *de novo* methyltransferases (DNMT);
  - DNA methyltransferase 3 (DNMT3);
  - And upheld by DNMT1 (the maintenance methyltransferase).

In general, DNMTs are three-dimensional proteins with motifs I-X located in the carboxyl end of the structure. The motifs have a specific function, as listed below:

- I and X form the SAM binding site;
- IV has a prolylcysteinyl dipeptide providing the thiolate at the active site which mediates the exchange of a methyl group from the SAM onto the cytosine;
- Between VIII and IX one can find the target recognition domain;
- VI protonates N3 points of the targeted cytosine by a glutamyl residue.

There are three big families of DNMTs; DNMT1, 2 and 3. The 1 and 3 families have members with definite function at CpG sites and islands, whereas DNMT2 is lowly expressed within all tissues and has an undetectable activity. Nonetheless, its activity seems to be present *in vitro* and it can catalyse RNA methylation [15].

There are 2 occurrences of *de novo* DNA methylation at the developmental stage of an embryo after demethylation episodes have taken place which erase the imprints established by the former generation. One occurs as early as right after embryonic implantation and affects the cells of the embryoblast. This epigenetically differentiates the embryoblast from the trophoectoderm. The 2nd occurs in primordial germ cells (PGCs) after implantation. In females, methylation levels in PGCs drops by 70% and takes place at oocyte growth phase postnatally while in males, levels drop by 60%, taking place just a few days after the 1st *de novo* reprogramming. The image below (**Figure 3**) gives an overview on the process of DNA methylation and histone modification mechanisms [8].

1.2.2. Abnormal DNA Methylation

One of the main functions of DNA methylation is to control the compartmentalisation of DNA. This guarantees the replication of specific sequences of transcriptionally active chromatin before the remaining transcriptionally inactive chromatin. Imbalance in the DNA methylation within cells can cause extensive hypomethylation, local hypermethylation and increase the cell's methylation capacity. Hyper- and hypo-methylation seem to affect different DNA sequences and it is apparent that much more of the genome is subject to hypo- than hyper-methylation.

Less or more methylation is relative. It is usually determined through comparison with a standard. The standard typically refers to normal tissue cells. Nonetheless, a great deal of variance is found in the quantity and distribution of DNA methylation amid different vertebral tissues. This is to say that DNA methylation is not just species-specific but also tissue-specific. In addition, uncultured cells should be taken for study whenever it is made possible as cultured cells tend to produce changes in their DNA methylation. Another issue to consider is that populations of pure uncultured cells may differ from each other by their genomic methylation content. Hence, unless the abnormally methylated cells are compared to a rather pure population of cells which are known to be the

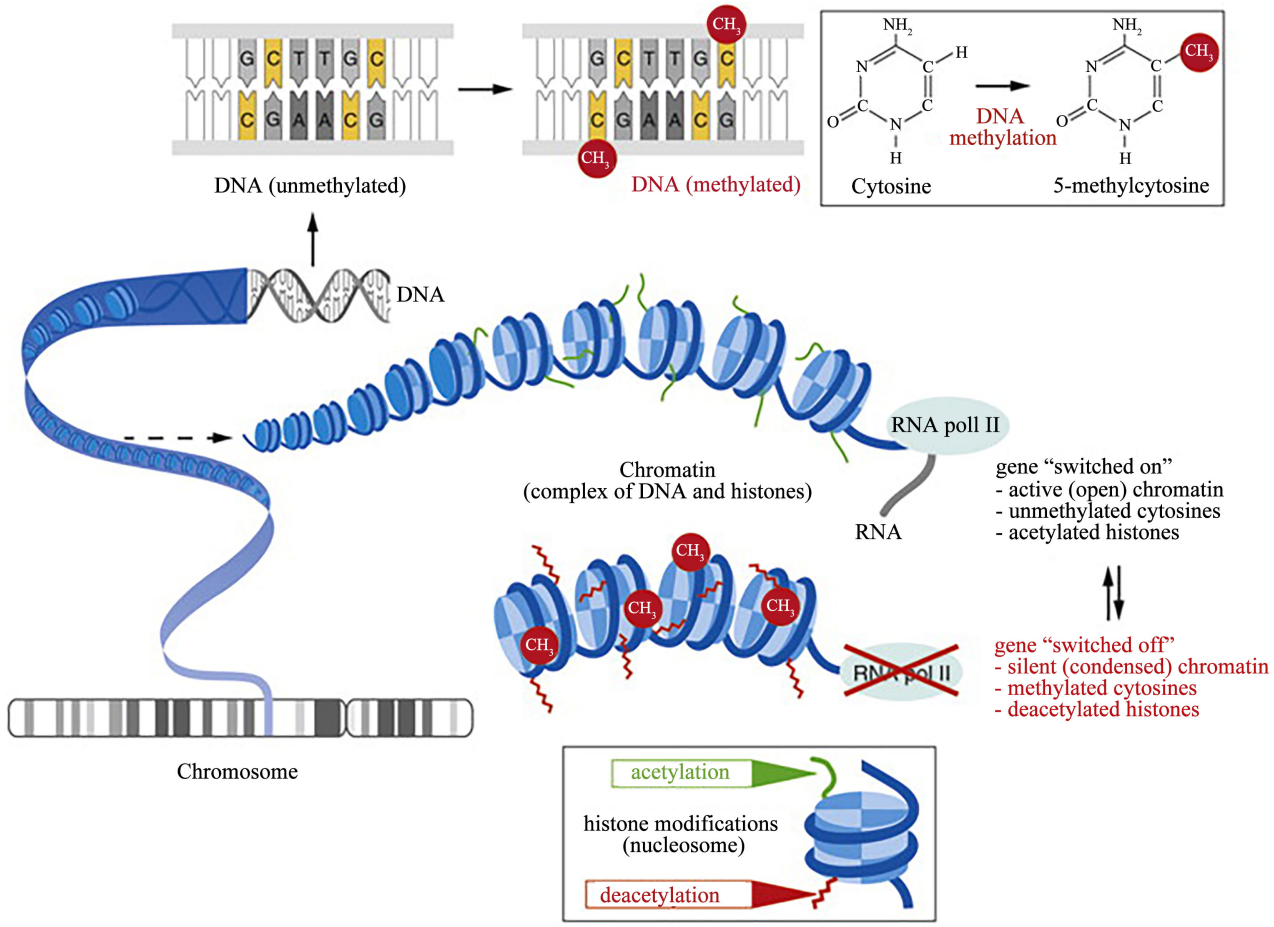


Figure 3. DNA methylation and histone acetylation on chromatin structure [16].

cell origin of the abnormal cells (which is almost never the case), it is always best to take an average of the methylation by taking DNA samples from cells across a multitude of tissues for the control.

Abnormal chromatin organisation is marked by, and many times caused by, the changed methylation patterns, particularly by regional hypermethylation. Following altered chromatin structure, increasing loss of gene expression may take place (as in the formation of tumours and other abnormalities) through direct transcriptional inactivation of genes, an increased predilection to mutations and deletion of alleles [17] [18].

1.2.3. A General Introduction on Imprinting

Everyone has 2 sets of 23 chromosomes, one from their mother and one from their father. Gene expression is usually dependent on whether a gene is autosomal dominant or recessive and its counterpart from the other parent.

Imprinting is a non-pathological process by which DNA expression is altered by means of external modifications and not direct DNA mutations. Thus, it is an epigenetic route of modulating gene expression. Imprinting is a hereditary influence that is either a maternal or paternal epigenetic altering factor which pertains to the modified gene expression [2] [3].

That is, imprinting will occur depending on whether it is inherited from the mother or father, parent of origin dependent methylation of DNA. So, when the maternal one is active, the paternal one is silent or vice versa. Hence, only 1 allele (either maternal or paternal) is expressed in the zygote. The "silent" or switched off allele is methylated so as rendering it unable to be transcribed. It is of crucial importance for mammalian development. Differentially methylated regions (DMRs), also known as imprint control regions (ICRs) are DNA methylation instances that occur in an allele-specific manner. Activity of gene in zygote depends on whether gene is from the mother or the father. It is a mono-allelic, parent-of-origin specific gene methylation and expression [19] [20].

In females, only one of the 2 homologous X chromosome is active. Imprinting ensures the selective expression of one of the chromosomes by methylation of the inactive copy [8].

Even though imprinting occurs in a very small portion of the entire genome, it contributes greatly to embryogenesis, reproduction and gametogenesis. Defects, disorders or relaxation in the imprinting process give a loss of imprinting on loci which are dependent on this process. In turn, this gives rise to rare diseases which affect growth, development, behaviour and metabolism which are associated with epigenetic distortion of imprinting genes [2].

1.2.4. Histone Modification

Acetylation and methylation of histones are the commonest types of histone modification. Euchromatin, the more active configuration of chromatin, is associated with high levels of acetylation and methylation at H3K4, H3K36 and H3K79. Conversely, heterochromatin, a much more condensed chromatin, is thus more associated with deacetylation and methylation of H3K9, K3K27 and H4K20 [8].

1) *Histone Acetylation/Deacetylation*

Acetylation is brought on by HAT proteins that belong to 3 families; GNAT, MYST and CBP/p30. In general, these preferentially target histones H3 and H4 for acetylation. They are able to acetylate both histone and non-histone proteins. Deacetylation occurs through the use of HDAC proteins that are also classified into 3 groups; type I, II and III. All 3 types bring about deacetylation of the N-terminal tails of histones where the acetylated residues reside, except in H3K59—found in core domain [8] [10].

2) *Histone Methylation/Demethylation*

Methylation is catalysed by histone methyltransferases (histone KMTases). In comparison to acetylation, methylation is a more complex type of modification. Methylation constitutes of 3 different states; mono-, di- and trimethylation. It can mark lysine and arginine and start or stop transcription based on the location and number of attached methyl-groups [8] [10].

3) *Histone Variants*

Histone variants are different from their respective canonical S-phase histones in ways that can lead to great chromatin differentiation. There exists the potential

of switching a chromatin state by histone replacement. Substituting one histone with a variant could also delete or change posttranslational modifications patterns, and therefore, can potentially reset epigenetic states that are thought to be mediated by histones and their modifications.

Histones H2A, H2B, H3, and H4 inhabit distinct locations in the core particle. Subsequent changes of the four core histones into distinct variants have provided the foundation for epigenetic routes, including development and chromosome segregation. The active behaviour of chromatin leads to the comprehension that transcription, chromatin remodelling, and histone modification might be combined with nucleosome assembly and disassembly. Histone variants are also entangled in particular epigenetic occurrences. For instances, the X chromosome has 3 different H2A variants which have been enlisted to participate in silencing or activation of genes for germline inactivation or dosage compensation [8] [11].

4) *Other Forms of Histone Modifications*

Less common histone modification mechanism are phosphorylation and ubiquitination. Phosphorylation is in control of decondensation of chromatin fibres, *i.e.* allowing for the activation of transcriptional activity but in contrast, also allowing for the compaction of chromosomes during cell division. With regards to ubiquitination, through this, histone proteins nearly double in size. Histones are usually mono-ubiquitinated. Poly-ubiquitination, much like methylation, gives rise to activation or repression of transcription depending on which histone protein undergoes ubiquitination [8].

1.3. The Involvement of Non-Coding RNAs in Epigenetic Processes

Non-coding RNAs (ncRNAs) have a role in transcription silencing, imprinting and amending heritable reactions to changes the environmental conditions the organism is exposed to. ncRNAs have been found to play major roles in processes such as cell patterning, differentiation, progression of cell cycle, stability of genome and apoptosis. Loss of ncRNAs would lead to downregulation of such important processes which can ultimately lead to various human diseases due to increased susceptibility.

Small regulatory RNAs are single stranded ncRNAs derived from complementary or semi-complementary double-stranded RNA (dsRNA) molecules and take part in transcriptional and post-transcriptional gene silencing, PTGS. PTGS is the downregulation of expression of the genome after transcription and mRNA maturation. Small RNAs are involved in a vast array of different functions in cell biogenesis including:

- RNA interactions—including with other small RNAs and mRNA
- Protein binding
- Direct reversible and irreversible changes to DNA and RNA sequences—methylation and genome editing respectively.

Long ncRNAs (lncRNAs) are less conserved in sequence and structure than

small ncRNAs, with some regions in the lncRNAs more conserved than others. This indicates towards more important sequences or structure recognition areas. lncRNAs transcription is regulated by developmental processes and differentiation. This accompanied with the knowledge that lncRNAs are restricted to certain compartments in the cell suggest an importance of lncRNAs in certain cellular processes. Such that, changes in their expression have been observed to lead to a variety of human diseases.

Other types of ncRNAs:

- microRNA (miRNA)
- small interfering RNA (siRNA)
- P-element-induced wimpy testes (PIWI)-interacting RNA (piRNA) [8] [21]

2. Epigenetics and the Environment

It is apparent that epigenetic alterations modulate molecular, cellular and organismal reactions to environmental changes. At every point in one's lifetime they are exposed to various physical, chemical and social agents that can have beneficial and detrimental interactions with the individual. A person's exact exposure to the environment, regarding duration, degree and type of environmental agent differs greatly from everyone else's, it is unique and ever changing.

Examples of environmental factors and their effect on health:

- Second-hand smoking—exposure is very directly linked to lung cancer development, or rather linked to a much higher susceptibility percentage to lung cancer development
- Socioeconomic status—different childhood status is associated with dissimilarities in common health indicators, like BMI and blood pressure
- Dietary content—bioactive food components such as in the agouti mice experiment
- Radiation exposure—direct/indirect radiation effects in tumour suppression inhibition

Figure 4 gives a concise overview on diverse environmental factors and their possible effects on epigenetics.

Environmental, epigenetics and phenotype and their relations are very clearly seen in the agouti locus in mice. The agouti loci are correlated to coat colour, obesity and cancer in mice and changes in parental diet so as to have a methyl content have proven to foster epigenetic changes in previously mentioned traits in offspring. **Figure 5**, found on the following page, demonstrates the agouti methyl-diet experiment [8] [22].

Environmental conditions that effect nutritional, physical and emotional health of a person can have long-term repercussions on metabolism and affective states in offspring—probably by action on promoter or enhancer related DNA methylation of the relevant genes.

Adverse environments in early childhood and parental care leave a long-lasting imprint on epigenetic regulation of steroid receptors and other genes, like

γ-aminobutyric acid (GABA). This is seen through detailed examination of the promoter structures of stress-related glucocorticoid receptor genes in humans.

Evidence shows that along with environmental toxins, diet and environmental enrichment might regulate phenotypic variations in following generations via germline transmission through the involvement of DNA methylation and histone alteration and small RNAs [24].

2.1. A Global Human Contribution—Air Pollution

Air pollution levels are always on the rise. The health risks (e.g. lung cancer) associated with it are thus, also on the rise. Examples of an air pollutant is black carbon—associated with cardiovascular morbidity and those related to cardiovascular disease. Asthma is principally related to air pollution which increases asthmatic episodes and susceptibility for onset of asthma.

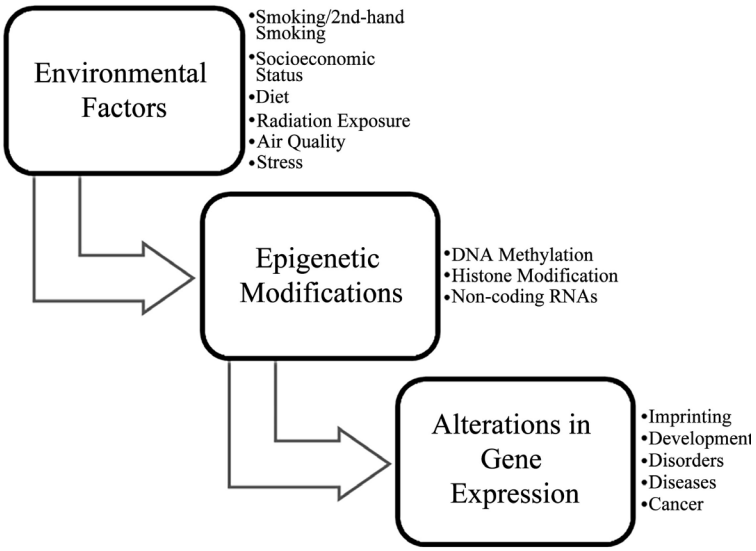
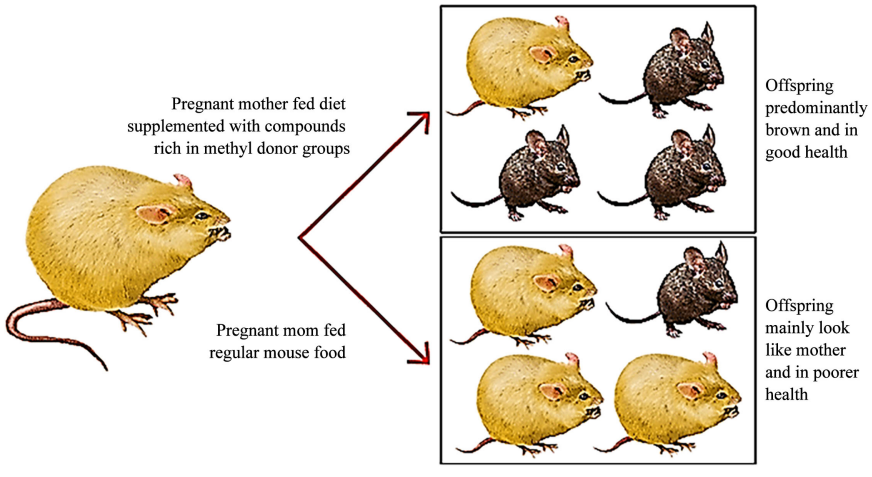


Figure 4. A Flowchart depicting an overview on the effect of the Environment on Epigenetics.



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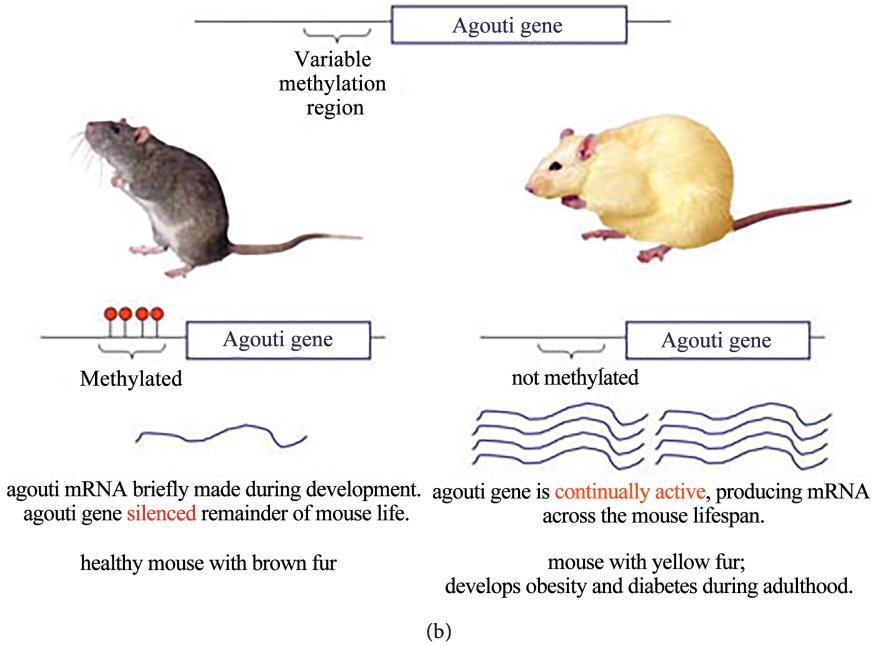

Figure 5. Methyl diet and normal diet differences in agouti mice. The yellow coated, obese mice are also predisposed to cancer and diabetes [23].

Regulatory T cells (Treg) is involved in development and advancement of asthma. Its activity may be modified my DNA hypermethylation. A study examining relations between asthma, air pollution and epigenetics brought credit to the notion that air pollution affects DNA methylation which impairs Treg function which in turn progress the pathogenesis of asthma [8].

2.2. Psychological Environment

Another environment to consider is the psychological environment. Stress is a reaction to threats the organism feels exposed to in an environment. It gives both behavioural and psychological stress responses. Stress is nowadays associated with very negative ideas. However, the purpose of stress is to respond to it in a way that makes the individual cautious around dangerous situations and it is thus critical for ensuring good health and survival [8] [21].

Nevertheless, there is something as too much stress, a state most people are too familiar with. Exposure to stress early on in life is closely related to negative effects on growth and intellect in conjunction with increased risks of obesity and mental illness. Additionally, stress later in life can result in adverse effects as well, such as a traumatic experience triggering the development of PTSD [25] [26].

2.3. The twin Model in Epigenetics

Monozygous twins, *i.e.* identical twins, provide an irreplaceable model for study of the effect of environmental factors on an organism. In essence, twins start out with similar epigenetics. As they grow older differences start to emerge. The

more time they spend apart and the more drastic differences there are in their respective environments and lifestyles, the greater segregation and differentiation observed in their epigenetics that can affect anything from the appearance of wrinkles to the predisposition to diseases [8] [27].

3. Epigenetics in Neuroscience

Research has shown that neurological processes are regulated by epigenetic component like DNA methylation, histone modification, chromatin remodelling and ncRNAs. Such processes that epigenetics influences include neuron development and function, neuronal plasticity and memory formation [8].

There is a bountiful amount of information supporting further investigation into the epigenetics in neuroscience. This includes the following ideas:

- Plasticity throughout all brain development and aging of most epigenetic markers with continuous and constant regulation in neurones;
- Therapeutic potential of epigenetics in neurological and psychiatric diseases. For example, histone deacetylation inhibition by chromatin-modifying drugs which exert great effects on learning, memory and neurodegenerative disorders;
- Transgenerational epigenetic inheritance—certain behavioural experiences during one's life can consequently be carried on to offspring. Nutrition, emotional and physical health of parent (environmental conditions) may have long-term results on the following generation at the same sites as the parent. Promoter or enhancer-related sites of the relevant genes on the genome are most probably affected epigenetically by methylation modifications [24].

3.1. DNA Methylation

At brain development, DNA methylation has a hand in the regulation of the proliferation of neuronal stem cells and their differentiation into glial cells and neurons. DNMTs are highly expressed throughout the developmental stage and uphold survival and plasticity of the neurons. In addition to DNMTs, methyl-CpG binding domains (MBDs) are shown and they also have a role in brain development with further activity in cognitive functions like learning and memory. DNA methylation has also been found important in adult CNS neurons (for the same functions as previously listed) and not just in the developing brain [8].

3.2. Histone Modification and Chromatin Structure

A holistic understanding of histone modification and chromatin structure remodelling can provide important insight on how stable gene expression changes in the brain can produce long-lasting alterations in behaviour. Neuronal signalling seems to be regulated greatly by histone acetylation/deacetylation and DNA methylation/demethylation.

Formation of long-term memory has seen to depend on chromatin remodelling by post-translational histone protein alteration. Furthermore, disruption in

the balance between HDAC and HAT activities can result in neurodegenerative diseases. HDAC inhibitors, *i.e.* blocking the removal of acetylation from the N-terminal histone tails, have been proven to show a therapeutic effect on animal models with neurodegenerative diseases insinuating a neuroprotective role [8] [10].

3.3. The ncRNAs

The ncRNAs make up approximately 98% of the transcriptional activity of genomic DNA. They don't behave as mRNA, tRNA or rRNA. A particularly abundant type of ncRNA in the brain is miRNA. miRNAs have a role in gene expression regulation through an RNA interference pathway that alters mRNA stability and initiation of translation. One miRNA is capable of regulating thousands of different mRNA targets. They are involved in cellular development, differentiation, proliferation, cell division and apoptosis amongst other biological processes and they are found entangled with onset and progression of cancer and other diseases.

In the brain, spatial and temporal expression of miRNAs in the nervous system hint that regulation of them might be of significance to neuronal development and function. The expression of these ncRNAs is dependent on various factors and can be kept in check by DNA methylation and chromatin structure, other epigenetic mediators [8].

3.4. Epigenetic Influence on Psychiatric Disorders

Genetics is thought to be the originator of psychiatric disorders but currently specific gene mutations have yet to be identified as inducers to psychiatric disorder development. On the other hand, copious research gives evidence towards the epigenetic involvement in pathogenesis of major psychiatric disorders, both hypo- and hyper-methylation.

A grand-scale complete methylome (set of methylation modification of nucleic acids in genome) analysis has brought to the surface global patterns of normal brain methylome, schizophrenia-patient and depression-patient brain methylomes. Methylome DB (Diabetic Retinopathy) was first to provide a comprehensive source of brain methylome data encompassing DNA methylation profiling of the whole human genome in addition to schizophrenia and depression methylome investigations [12].

What's more, histone lysine methylation alterations have demonstrated contributions to modifications in brain transcriptomes, affecting mood and psychosis spectrum disorders (such as depression and schizophrenia). In recent studies, miRNAs have also been suggested as having roles in psychiatric pathologies. The studies exhibited significantly altered miRNA patterns in the prefrontal cortex of schizophrenic and bipolar patients.

Hence, epigenetic changes are now thought to be the chief regulators of standard brain development and function and thus also significant influences in a large spectrum of neurological and psychiatric disorders. This information

makes epigenetic alterations at the centre of the study of future psychiatric therapies [8].

4. Depression

4.1. A Basic Overview

Clinical depression is a serious psychiatric disorder that is characterised by a vast array of symptoms that may not all be present within an individual. It can affect how a person thinks, feels, acts, the person's sleep patterns, eating or working.

There are various types of depression including:

- Persistent depressive disorder
- Postpartum depression
- Psychotic depression
- Seasonal affective disorder
- Major depressive disorder—which is mainly what is going to be discussed
- Bipolar disorder—this doesn't indicate that it is a type of depression but a person with bipolar disorder can experience extreme lows with symptoms that meet the criteria for major depression.
- Disruptive mood dysregulation disorder
- And premenstrual dysphoric disorder.

[28] [29] [30]

For diagnosis of depression the patient must be experiencing the associated symptoms for at least 2 weeks. Symptoms that a patient can normally present with are:

- Persistent sadness, anxiety or feeling emptiness
- Hopelessness or pessimism
- Increased irritability
- Feelings of guilt, worthlessness or helplessness
- Reduced energy or fatigue
- Slowed down movement or talking
- Restlessness
- Concentration or memory issues
- Indecisiveness
- Sleep irregularities—early-morning rising or oversleeping
- Appetite or weight changes
- Suicidal thoughts or attempts
- And pain—headaches, cramps or digestive issues that don't seem to have a cause or don't clear up after treatment.

[28] [31] [32]

4.2. Risk Factors

Depression is caused by an amalgamation of genetic, biological, environmental and psychological factors. Epigenetic being one such determinant of depression. Depression can occur at any age but it is more often in adulthood. Experience of

high anxiety as a child, early-life stress (ELS), can start up a chronic mood and anxiety disorder in adulthood. However, depression may still present in children and teens, though presentation of irritability is more noticeable rather than a low mood [33] [34].

Certain serious illnesses much like Parkinson's disease and cancer can bring with them depression by their very nature. On presentation of depression, the effects of these diseases on the patient are often worsened.

A personal or familial history of depression will increase the likelihood of obtaining depression as well as drastic life changes, trauma and stress. Along with certain illness, some medications can increase the probability of developing depression [28] [31] [32].

Other medically related risk factors include:

- Being female
- Side effects
- Premenstrual hormone level changes
- Suffering from a long-term or serious illness—Stroke, vitamin B_{12} deficiency, hypothyroidism, hepatitis, HIV and some cancers
- Having another psychiatric disorder
- Alcohol or drug withdrawal.

Risk factors related to lifestyle or life events:

- Being a more sensitive, emotional and anxious person
- Adverse childhood experiences such as abuse or lack of care
- Living in poverty and in correlation having a poor education and social disadvantage
- Recent negative events such as being a victim of crime or abuse, experiencing a death of a close relation or being newly separated or divorced.
- Lack of a close confiding relationship
- Having a baby
- Alcohol or drug intoxication
- Lack of bright light exposure, especially sunlight in the winter months. [35]

4.3. Treatment and Therapy

Depression is a treatable condition, in even the worst-off cases. That said, the earlier a patient starts the treatment, the greater its effect. Normal first-line treatment in depression is psychotherapy and then medication or a combination of the two. If a reduction of symptoms is not observed, electroconvulsive therapy (ECT) amid other brain stimulation therapies may be considered.

In line with professional help, lifestyle changes such as regular exercise has been shown very effective in the recovery processes, however, only in conjunction to professional help [35].

4.3.1. Psychotherapy

Psychotherapy also referred to as talk therapy is basically an ongoing discussion

between the patient and psychiatrist. Per the type of depression a patient presents with, a specific psychotherapeutic approach is taken. Such evidence-based approaches are cognitive-behavioural therapy (CBT), interpersonal therapy (IPT) and problem solving therapy [28] [31] [32].

4.3.2. Medications

Antidepressants are the main form of medication used to treat depression. They have been found very effective with adults who have moderate to severe depression as they can help improve how the brain uses its neurotransmitters that effect mood or stress. There is an extensive lection of anti-depressants available and a patient may need to try out various types to find the most effective one for them with the least cumbersome side effects. If one has been diagnosed with depression before or a close relative has, the medication used then is a top consideration [28] [31] [32] [35].

Medication takes about 2 to 4 weeks for the patient to start experiencing alleviation of symptoms. Certain symptoms such as sleep, appetite and concentration problems improve before any changes in mood occur. Thus, time should be allowed before reaching a conclusion on the effectiveness of the therapy provided. As the patient's condition progressively improves, the patient with the approval and guidance of a medical professional can slowly wean the patient off the drug until sides of depression alleviate and stopping medication altogether would be the likely course of action in the management of the patient.

Antipsychotic medication is usually used for treatment of bipolar disorder, nevertheless it can sometimes be used against severe depression in combination with antidepressants when other forms of treatment haven't taken effect [35].

It is important to note that suicidal thoughts and attempts can increase during the first few weeks of therapy for children, adolescents and adults under 25. Hence, especially when first starting medication extra care should be taken by the professional to ensure safety of patient [28] [31] [32].

4.3.3. Brain Stimulation Therapies

ECT has been proven effective for people with severe depression who didn't respond well to other treatment options. It is the most acutely effective treatment for people with severe depression. Nevertheless, it has been seen to have adverse effects on the patient, such as confusion, disorientation and memory loss. The side effects are in the most part short-term however can linger especially in the months following the treatment. ECT may also be used as a first-line intervention in extreme cases where rapid intervention is required or use of medication is not advisable or safe. The procedure can be performed on an outpatient basis and constitutes a series of sessions usually along a 2 to 4 week period, 3 times a week. The patient is anaesthetised before the ECT begins, even though treatment is not painful and the patient doesn't not feel the electrical impulses. Hence, the term electroconvulsive is no longer accurate since an anaesthetised patient does not convulse. **Figure 6** is portraying a typical ECT session [28] [31] [32] [35].

Transcranial magnetic stimulation (TMS) is also considered when no other treatment has proven effective. The procedure involves holding a potent magnet over the scalp to stimulate some areas of the brain. The below illustration, **Figure 7**, demonstrates TMS [28] [31] [32] [35].

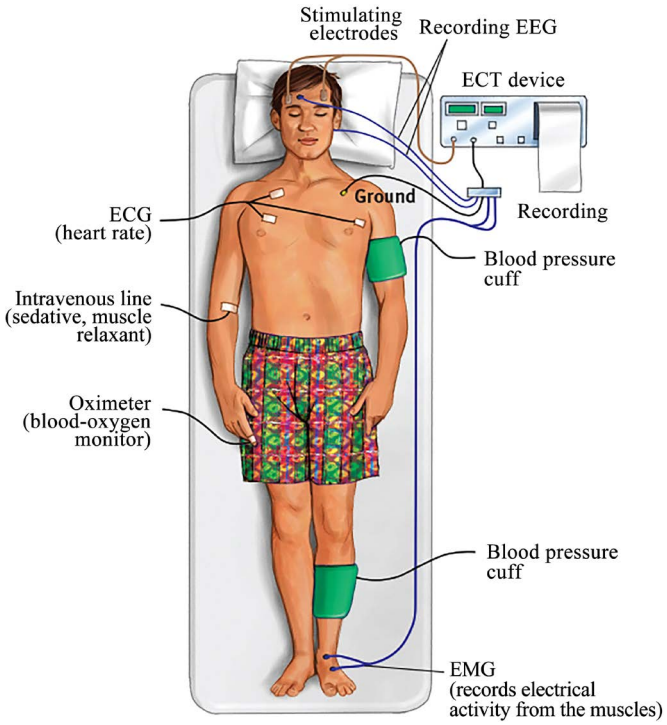

Figure 6. Typical set-up of an ECT session [36].

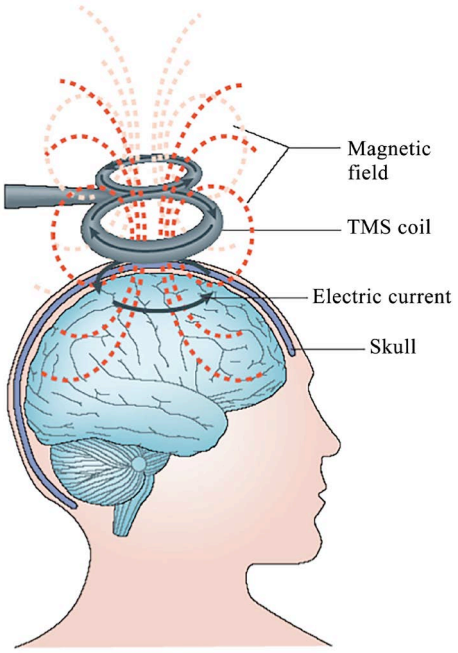

Figure 7. Image illustrating the induction of electrical currents in the brain (black arrows) through the magnetic pulses (red/pink) applied by means of the coil [37].

5. Depression Epigenetics

5.1. Risk Factors

The heritability of major depressive disorder (MDD) is around 31% - 42% yet research has failed to show evidence of gene loci that contribute to the disorder. In addition, a high discrepancy of 50% between identical twins is suggestive of factors other than genetic ones contribute to the disorder.

Environmental stressors have been brought to light as risk factors with still varying susceptibility to the environmental stimuli from one individual to another. As MDD cannot be accredited to a specific gene mutation or exposure to a specific environmental cause, the theory that MDD arises from alterations in the genome brought about by external factors is favoured greatly.

Epigenetics is therefore, a major possible mechanism by which environmental stimuli such as stressors can have persisting modifications in gene expression. In rodent models, gene expression alterations have been reported following exposure to acute stress, chronic stress, fear conditioning and post-traumatic stress disorder. Furthermore, epigenetic modifications brought on by ELS show that emphasis should be made on the epigenetic mechanisms related to the pathogenesis of MDD in humans. Evidence supports the indication that negative stimuli presented early in life can affect behaviour in adulthood and consequently, predispose individuals to mental illnesses such as depression amongst susceptibility to other health problems [38].

Early Life Stress

DNA methylation and histone modification at the promoter sites on genes, for example brain derived neurotrophic factor (BDNF) which promotes neurogenesis, and miRNA expression pattern changes have been seen after prenatal, perinatal and postnatal stress.

DNA methylation pattern changes involved in depression include:

- BDNF
- Glucocorticoid receptor
- And serotonin transporter.

These have been found prevalent in children who were prenatally exposed to stressors from mother such as smoking, depression and stress from abusive partnership or war. Negative experiences in early childhood like being a victim of child abuse show that the epigenetic influences (such as methylation) on the glucocorticoid receptor and the rRNA promoter were altered—through investigation of the post-mortem brains of suicide victims with experience of abuse as children. What's more, early life poverty and low socioeconomic status show a DNA methylation.

The exposure to a mix of various pre- and post-natal stressful stimuli is associated with epigenetic alterations to depression related gene loci in rodents and also in humans. These epigenetic modifications are why ELS may take long-term effects on a person and their offspring—even though they themselves have not experienced the trauma, meaning also they can be further passed on to more

generations down the line. Transgenerational phenotypic transmission is underlined by environmentally produced stable, persistent epigenetic changes in gene expression [34] [38] [39].

1) *BDNF*

Methylmercury exposure during gestation shows increased depressive-like behaviour in mice. The exposed mice had a decreased hippocampal mRNA of the BDNF through increased methylation and decreased histone acetylation of BDNF gene promotor region. Postnatal stressors, such as lack of or reduced maternal care, give rise to decreased BDNF transcription in prefrontal cortex which was followed up by increased suppression of BDNF promoter site in adulthood because of higher DNA methylation levels. This effect was found to be reversible by the administration of a DNA methyltransferase inhibitor, zebularine. **Figure 8** gives an overview on the effects of methylation [38] [40] [41].

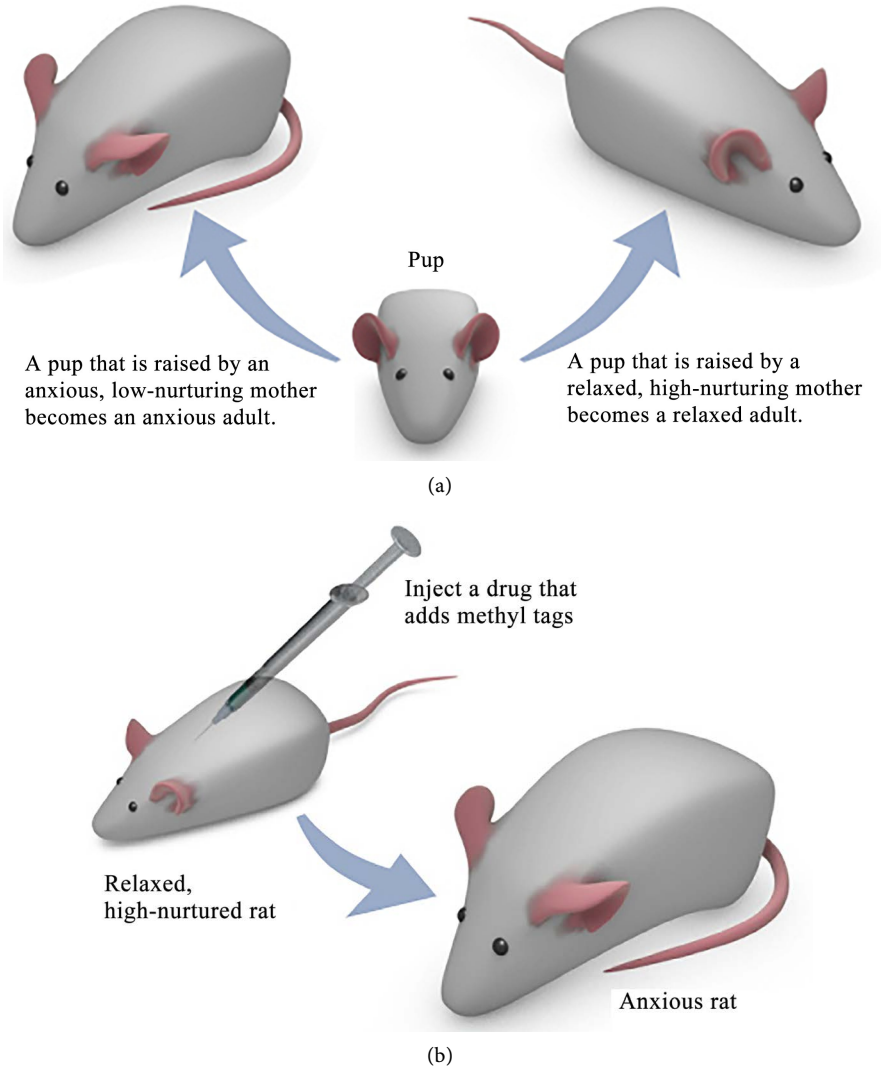

Figure 8. A pup grows up to be anxious or relaxed depends on the mother that raises it not the one that gave birth to it (a). Proof of methylation effect on behaviour through epigenomic change rather than genomic (right) [42].

5.2. MDD

Depression-related genes, for instances GABA receptor subunits, serotonin transporter, mRNA expression of epigenetically involved enzymes and synapsins have been studied along with genome-wide DNA methylation patterns in MDD patients. Certain importance has been placed on BDNF pathway due to its observed epigenetic modification in MDD.

BDNF promoter methylation *i.e.* decreased BDNF mRNA levels in Wernicke's area was discovered in suicide victims a portion of whom were diagnosed with MDD. However, DNA methylation and mRNA expression of the BDNF receptor, Trk B, in Wernicke's area was not found to be modified. Instead, the receptor was found in decreased levels within the prefrontal cortex in relation to increased CpG site and histone 3 methylation at Trk B promoter region.

Evidence also indicates that miRNA regulation of proteins in MDD patients was decreased and reorganised in comparison to control individuals. Changes in; miRNA levels; polymorphisms in miRNAs and their precursors; the miRNA targeted mRNA; and in the miRNA biogenesis regulator genes are observed in MDD.

DNA methylation, histone alteration and miRNA expression changes are greatly involved in the disruption and dysregulation of gene expression in depression. Better understanding of the mechanisms of depression pathogenesis opens doors to improved diagnosis and specific targeted treatment [38] [43].

5.3. Treatment and Therapy

5.3.1. Medications

Regardless of epigenetics' role in depression pathogenesis, epigenetic alterations of gene expression aid in the mechanisms antidepressant medication action. Changes in DNA methylation, miRNA activity and chromatin activation status were observed when comparing the data of before and after antidepressant administration preclinical and clinical investigations.

A particular study showed that antidepressant treatment of social defeat stress in mice (its symptoms mimic depressive symptoms in humans) with imipramine, results in increased mRNA levels for BDNF which were previously reduced on presentation of the disorder.

Collectively, the data from human and animal models put forth the suggestion that antidepressant treatment reverses the alterations to the epigenome or introduces alternative compensatory epigenetic mechanisms (e.g. histone hyperacetylation and DNA hypomethylation) which promote expression of previously repressed genes.

Garnering a more holistic understanding of epigenetic action in antidepressant mechanisms may direct development of novel MDD treatments, such as targeted HDAC inhibitors, DNA methyltransferase inhibitors and miRNA inhibition with small molecules. More so, expression patterns of miRNA can possibly serve as valuable biomarkers in prediction of the individual's response to treatment [38] [40] [44].

5.3.2. Brain Stimulation Therapies

The precise mode of action of ECT is unknown, however, evidence points towards the mechanisms of epigenetic modification of gene expression. Examined changes in rat hippocampal BDNF at different time intervals during electroconvulsive stimulation (ECS—the animal equivalent of ECT) indicate that the resulting histone modifications on BDNF gene expression depend on treatment duration, post-treatment time and the gene promoter region. Histone modification and related mRNA alterations of CREB (cAMP response element binding protein) and c-Fos (a proto-oncogene expressed in some neurons following depolarisation) as well as elevated DNA methylation at the Arc promoter also result from the use of ECS in the animal model.

These findings strengthen the idea that epigenetic changes of gene expression have a key role in the action of ECT as a powerful form of anti-depressant treatment, even though human model testing has yet to be investigated [38] [39] [44] [45].

6. Conclusions

It is safe to say that epigenetics requires more time and research dedicated to it. Epigenetics is a word that spans a great number of concepts, mechanisms and theories. In this paper, only the tip of the tip of the iceberg that is epigenetics has been discussed. Attention has been brought to the fact that each mechanism of epigenetics is affected by different stimuli and affects different aspects of the genetic material. Disruption in the balance between HAT proteins and HDAC proteins mediating histone acetylation and deacetylation can result in neurodegenerative diseases. Each mechanism has a basic effect on the genome, for example, DNA methylation inactivates a gene's expression and demethylation reverses this.

Our surroundings are major contributors to our epigenetic differences. Different stimuli result in diverging epigenetic modifications which can be stable and persistent for an entire lifetime. However, the modifications are reversible through exposure to other stimuli or through specific epigenetic targeting drugs. Increased depressive behaviour due to methylmercury exposure in mice is reversible by a DNA methyltransferase inhibitor. Moreover, even though reprogramming occurs at gametogenesis to remove parental epigenetics, transgenerational epigenetic contributions may still occur, causing a transference of an "ancestral memory" which can affect anything including behaviour and vulnerability to physical and mental health problems.

Over and above this, epigenetics with respect to depression is reviewed. Imipramine administration to mice with social defeat stress increases the previously reduced mRNA levels for BDNF. Human models on the topic are few and far in between but those that are available confirm many of the animal models and the speculations on their application to the human epigenetic mechanisms. Through the animal and human studies, theories on new antidepressant therapeutics are being investigated and the promise of more specific and effective

medication is over the horizon. The epigenetic rabbit hole is a dark and vast space which has yet to be brought to light and its walls have yet to be reached.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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