Review Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2023; 15(1):132-145
doi: 10.18863/pgy.1059315

Epigenetic Effects of Social Stress and Epigenetic Inheritance

Sosyal Stresin Epigenetik Etkileri ve Epigenetik Kalıtım

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ABSTRACT

Social events that cause stress can cause epigenetic changes on living things. The study of the effects of social events experienced by an individual on epigenetic marks on the genome has created the field of social epigenetics. Social epigenetics examines the effects of psychosocial stress factors such as poverty, war trauma and childhood abuse on epigenetic mechanisms. Epigenetic mechanisms alter chemical markers in the genome structure without changing the DNA sequence. Among these mechanisms, DNA methylation in particular may have different phenotypic effects in response to stressors that may occur in the psychosocial environment. Post-traumatic stress disorder is one of the most significant proofs of the effects of epigenetic expressions altered due to traumatic events on the phenotype. The field of epigenetic inheritance has shown that epigenetic changes triggered by environmental influences can, in some cases, be transmitted through generations. This field provides a better understanding of the basis of many psychological disorders. This review provides an overview of social epigenetics, PTSD, and epigenetic inheritance.
Keywords: Social epigenetics, stress, DNA methylation, post traumatic stress disorder

ÖZ

Stres oluşturan sosyal olaylar, canlı üzerinde epigenetik değişimlere sebep olabilmektedir. Bir bireyin sosyal açıdan yaşadığı olayların genom üzerindeki epigenetik işaretlere olan etkisinin incelenmesi, sosyal epigenetik alanını oluşturmuştur. Sosyal epigenetik; yoksulluk, savaş travması, çocukluk dönemi istismarı gibi psikososyal stres faktörlerinin epigenetik mekanizmalar üzerine etkisini incelemektedir. Epigenetik mekanizmalar DNA dizilimini değiştirmeden genom yapısındaki kimyasal işaretleri değiştirmektedir. Bu mekanizmalardan özellikle DNA metilasyonu, psikososyal ortamlarda oluşabilecek stres faktörlerine yanıt vererek farklı fenotipik etkiler meydana getirebilir. Travma sonrası stres bozukluğu (TSSB), travmatik olaylar sonucu değişen epigenetik ifadelerin fenotipteki etkilerinin en büyük kanıtlarından biridir. Epigenetik kalıtım alanı, çevresel etkilerin tetiklediği epigenetik değişimlerin bazı durumlarda nesiller boyu aktarılabildiği göstermiştir. Bu alan birçok psikolojik rahatsızlığın temelinin daha iyi anlaşılabilmesine olanak sağlamaktadır. Bu derlemede sosyal epigenetik, TSSB ve epigenetik kalıtım konularına genel bir bakış sunulmuştur.
Anahtar sözcükler: Sosyal epigenetik, stres, DNA metilasyonu, travma sonrası stres bozukluğu

Introduction

The epigenetic concept, which means "genetics over genes", is the change of chemical markers in the genome structure without a change in the DNA sequence. These changes that affect gene expression determine when, where and how much genes are expressed. The epigenetic mechanisms that enable these changes are DNA methylation, post-translational histone modifications and non-coding RNAs (Jenuwein and Allis 2001).

The question that combines the epigenetic field with social fields is whether the events of an individual's social experience change the epigenetic markers on the genome (Champagne 2018). In particular, the effect of social events that cause stress on the epigenetic modifications of living organisms has been examined by researchers. Increasing studies have started to introduce the concept of social epigenetics more frequently. Social epigenetic studies how socially defined experiences and situations can leave biological signs in the body through epigenetic mechanisms (Dubois and Guaspare 2020). In other words, social epigenetics examines the effects of psychosocial stress factors on epigenetic mechanisms. The impact of these effects on phenotype is focused on. Psychosocial stressors include many stress factors such as poverty, low education level, war trauma, childhood abuse, harassment, and racism (Mulligan 2016).

Social epigenetics, which is an interdisciplinary field of study, has gained attention from numerous national and

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Received: 24.01.2022 | **Accepted:** 17.08.2022

international organizations. For instance, in 2014, a workshop was organized with the support of the National Science Foundation and the Research Councils UK called "Social and Behavioral Epigenetics", where researchers in various areas, such as psychologists, biologists and sociologists were gathered. In 2016 and 2019, the National Institute of Health (NIH) called for a series of projects, titled “Social Epigenomics Studies”, focusing on Minority Health and Health Disparities and aimed at identifying mechanisms in which their positive and negative experiences in social life affect the gene function (Dubois and Guaspare 2020).

Since the beginning of the 21st century, the field of epigenetics has redefined trauma as a form of social exposure in its own right (Dubois and Guaspare 2020). Traumatic stress is a specific type of stress that results in a response to a person being exposed to a threatening situation. Traumatic stress can occur in a person for a long or short period of time. Depending on this period, there are two main trauma-related disorders: Post Traumatic Stress Disorder (PTSD) and Acute Stress Disorder (ASD). While the duration of acute stress disorder is quite short, a person's long-term discomfort is associated with post-traumatic stress disorder (Schnurr et al. 2002, Jawaid et al. 2018).

PTSD is a disorder that occurs as stress-related symptoms develop after a person experiences a high-threatening trauma. PTSD can be triggered by multiple psychosocial factors, such as sexual abuse, malnutrition, domestic violence, or witnessing the death of a close relative (Prakash et al. 2015, Howie et al. 2019). The environmental changes that the person is exposed to must be made permanent in order for the person to develop PTSD. Recent studies have shown that epigenetic mechanisms have very important roles in making the effects of trauma permanent in person (Zovkic and Sweatt 2013). PTSD is one of the greatest evidences of the effects of epigenetic expressions on phenotype, which are changed as a result of traumatic events. As a result of some clinical studies and animal experiments, certain situations in which epigenetic expressions that alter with the impact of the environment can be defined as hereditary gene expression changes have been observed. The transfer of the changes caused by environmental factors to next generations without any change in the DNA sequence has strengthened the idea that epigenetic inheritance plays a role in this process (Sarkies 2020).

A person's life experiences cause changes in gene expression and signaling pathways. It has been found that these result in long-term behavioral-cognitive changes in the person. As a result of some data obtained in recent years, it has become difficult to explain the inheritance of neuropsychiatric, immunological and metabolic disorders by only genetic factors. Even if the next generation is not exposed to the stressor that caused the trauma in the previous generation, it has been shown as a result of many studies that some of the epigenetic changes that occurred in the previous generation can be transferred to the next generations. The increased inherited risk of neuropsychiatric disorders in subsequent generations makes the correct understanding and definition of epigenetic inheritance even more important.

According to the definition of Park and Kobor (2015), social epigenetic is the study of molecular mechanisms that affect the gene expression of early life experiences and have permanent effects on human physiology and health. In this context, in our review, we included the biological response of early life stress in the body, the epigenetic modifications that change by the effect of psychosocial stressors, PTSD, which is thought to be triggered by these changes, and the field of epigenetic inheritance, which examines the transmission of changing epigenetic modifications over generations.

Stress

Various environmental stimuli called “stress” are factors that disrupt homeostatic processes. This concept was first used by Selye in 1956 to express the effects of any situation that threatens homeostasis (Neylan 1998). Stress can arise or intensify by external stimuli, particularly environmental factors, or internal stimuli such as physical disorders (Schneiderman et al. 2005). The repair of homeostasis against these stimuli or the capacity to respond in a way that removes the individual from the stressful environment is one of the most important physiological mechanisms underlying the survival effort in vertebrates (Spencer 2017).

The hypothalamic pituitary adrenal axis (HPA) and the sympathetic adrenomedullary (SAM) system respond to stress in an appropriate physiologic and behavioral manner. The SAM system has a direct effect on the target organ by secreting epinephrine to create the fight-or-flight response (Gunnar and Quevedo 2007). The HPA axis is activated during and after the development process in adverse conditions. Stress stimulants cause the release of corticotrophin-releasing factor (CRF) from the hypothalamus to promote the secretion of the adrenocorticoid hormone ACTH from the pituitary gland (Wingfield and Romero 2001). ACTH then causes the synthesis and release of glucocorticoids (GC) from the adrenal cortex, stimulating their various physiological changes in

different tissues. These glucocorticoids, which are secreted in response to stress, cause psychological changes such as increased blood pressure, heart rate, and blood sugar (Yurdakök and Çelik 2019).

Stress exposure during pregnancy increases the amount of GCs (cortisol in human), which is the latest product of the HPA axis. Cortisols can affect processes such as pre- and postnatal brain development and HPA axis functions by passing from the placenta to the fetus (Harris and Seckl 2011). In addition to its short-term effects on HPA axis response and GC production, exposure to social adversity during development can have lasting effects on HPA function and regulation (McCormick and Mathews 2010). Social stressors may cause radical changes in the HPA axis both in the short and long term (Spencer 2017). There are studies showing that negative experiences, particularly in newborns, lead to increased DNA methylation in glucocorticoid receptor genes via the HPA axis, which in turn alters stress responses and behaviors later in life (Turecki ve Meaney 2016).

Early life stress may be a risk factor for a person's physical and mental development later in life. The more severe effects of adverse situations during an early period of life can result in a rise in the occurrence of many disorders, such as schizophrenia, the risk of depression, and post-traumatic stress disorder in people with this kind of history. Results gathered from studies with children showed that 61.8% of young people had experienced any trauma by the age of 17, and up to 5% of children under the age of 18 had symptoms of PTSD. As a result of a study conducted with a group of people who were abused in childhood, the detection of changes in the expression of multiple DNA methylations clearly shows that early life stress affects epigenetic changes. It suggests that epigenetic changes caused by early life stress can play a direct role in changes in PTSD physiology by causing disruption of neurobiological pathways that are involved in stress response (Pervanidou et al. 2020).

Epigenetic Mechanisms

Trillions of cells in multicellular organisms have the same DNA. The programming that makes these cells different and enables them to perform different functions is the result of epigenetic modifications. Epigenetic modifications occur during pre and postnatal development as well as throughout the rest of the life, and therefore result in changes in gene expression (Murgatroyd and Spengler 2011). Epigenetic effects are defined as phenotype changes that do not impact the DNA nucleotide sequence. Epigenetic modifications may be induced by environmental conditions during early embryonic stages. Epigenetic modifications altered in this way can be passed down through generations if they occur in the germline (Klose and Bird 2006, Burggren 2015). Non-coding RNAs will not be mentioned in this review.

DNA Methylation

Epigenetic mechanisms dynamically respond to many environmental cues such as nutrition, climatic and seasonal conditions, and the social environment (Beck et al. 2017, Cavalli and Heard 2019, Kubsad et al. 2019). DNA methylation from these epigenetic mechanisms is an important epigenetic modification that responds to a wide variety of psychosocial and biological stress factors that change throughout life (Mulligan, 2016).DNA methylation is performed by DNA methyltransferases (DNMT). DNMT1 is responsible for maintaining DNA methylation during cell division. DNMT3A and DNMT3B catalyze de novo methylation. These enzymes perform methylation by adding a methyl group to cytosines in CpG dinucleotides. DNA methylation has important functions such as genomic suppression during embryogenesis, inactivation of the X chromosome, and silencing retroposons. It is also dynamically modulated throughout the life (Guerrero et al. 2020).

50-60% of the CPG dinucleotides are in the promoter regions (Kanwal 2012). When methylation occurs in the promoter region, it is generally associated with the suppression of transcription (Glaser and Kiecolt-Glaser 2005). Initially, DNA methylation was associated with the silencing of genes, however subsequent studies have suggested that DNA methylation is associated both positively and negatively with gene expression, depending on a particular gene and part of the gene (Jones 2012).

De novo DNA methylation describes the process of adding methyl groups to unmethylated DNA at specific CpG sites (Okano et al. 1999). DNA methylation is very sensitive to environmental stimuli during early embryogenesis, which is known to be highly active in de novo methylation (Moore et al. 2012). There are many studies that establish the relationship between early life stress and DNA methylation. However, DNA methylation on the enhancer regions of the gene is considered to be more sensitive to variable and environmental stimuli throughout life (Johansson et al. 2013). Therefore, social epigenetic fields of study include epigenetic programming that starts with embryogenesis and varies throughout the life.

Histone Modifications

Two of each histone protein, H2A, H2B, H3 and H4, are wrapped around 147 bases of DNA twice, and this packaging unit is called the nucleosome. In this way, the DNA-protein complex consisting of both histone and non-histone proteins is called chromatin. Heterochromatins are tighter, denser, and transcriptionally inactive; euchromatins are looser and transcriptionally active (Kanwal and Gupta 2012). The accessibility of these chromatins is controlled by histone modifications. Post-translational histone modifications are covalent modifications that occur at the amino terminal tails of histone proteins. Some of these modifications are acetylation, methylation, phosphorylation, and ubiquitylation (Bannister and Kouzarides 2011). Histone acetylation is one of the most investigated modifications. Histone acetylation is the attachment of an acetyl group to the lysine residue in the amino terminal tails of histones by histone acetyltransferases. The addition of acetyl groups neutralizes the positive charge of lysines and weakens the interaction between histone and DNA. Therefore, this makes DNA available and allows transcription to occur (Bannister and Kouzarides 2011). Histone methylation occurs in the arginine and lysine side chains of histone tails. A methyl group is transferred to these amino acid residues by methyltransferases. Both lysine and arginine methylations may act as activators or repressors during transcription (Kouzarides 2007). However, the relationship between post-translational histone modifications and transcription is complex and there are many unknowns. Studies continue to enlighten these relationships.

Epigenetic Responses to Psychosocial Environments

Since most of the current studies on epigenetic and psychosocial stress are on DNA methylation, studies in the context of DNA methylation changing in psychosocial environments are included under this title. There are studies conducted by taking samples from people or their descendants exposed to various stressors, as well as studies examining rodents exposed to certain stressors. Buccal swab, blood and stool samples allow the collection of cells derived from different layers of the embryo (endothermal, ectodermal and mesodermal) and thus the examination of epigenetic changes. However, differences in epigenetic profiles in tissues and cell types may cause difficulties for studies (Waterland and Michels 2007). At the same time, it is also considered that the expected results may be obtained because the thing to be examined is not a fixed amount of expression, but a potential range (Landecker and Panofsky 2013).

The methylation changes of genes linked to the HPA axis have been investigated in the context of early life stress. In particular, methylation of the NR3C1 gene encoding the GC receptor has been widely studied for its important role in the HPA axis response to early life stress (Turecki and Meaney, 2016). Oberlander and colleagues (2008) performed one of the first studies of methylation of the NR3C1 gene encoding the GC receptor in humans. When a developing fetus is exposed to maternal stress, increased methylation of the infant's NR3C1 promoter has been found after birth. Rodney and Mulligan (2014) examined NR3C1 methylation in mothers and infants from the Democratic Republic of Congo, where psychosocial stressors such as war are present and they found a methylation increase in the NR3C1 promoter of newborns. In another study (Radtke et al. 2011), methylation of the GR gene was examined in the children of mothers who were exposed to partner violences after 10–19 years and, a positive association was found between GR promoter methylation in children and maternal exposure to partner violence during pregnancy. Studies show a strong relationship between early life stress and NR3C1 promoter methylation.

Another important point is that the NR3C1 methylation is associated with psychological diseases. According to a systematic review study on NR3C1 methylation and psychosocial stress, the methylation profiles of some exons of this gene may be a biomarker related to the psychopathological phenotype (Palma-Guidel et al. 2015). In this context, the NR3C1 promoter methylation level and timing may be critical at the point of predicting disease risk in the future (Palma-Gudiel et al. 2015, Turecki and Meaney 2016).

Studies were not limited to the NR3C1 gene, CRH, CRHBP, and FK506 genes, which regulate the HPA system, were also investigated in terms of changes in DNA methylation caused by psychosocial stressors, and evidence was presented regarding the relationship between DNA methylation and exposure to prenatal stress (Klengel et al. 2013, Xu et al. 2014). In order to assess the impact of chronic stress and war trauma, the methylation profiles of the CRH, CRHBP, NR3C1, and FKBP5 genes of 24 mother-newborn couples in the Democratic Republic of the Congo's conflict region were studied. (Kertes et al. 2016). The methylation alterations were detected significantly in the transcription factor binding sites of target genes when samples from maternal blood, cord blood, and placenta tissue were investigated. Significant correlations were found between methylation levels of the four genes and stressors in placenta and maternal blood. Stress exposure is associated with an increase in methylation

in the CRY gene. In this context, the HPA axis shows the relationship of the four genes with prenatal maternal stress.

The brain-derived neurotrophic factor BDNF is another gene affected by the HPA axis response. The increase in GC caused by stress may disrupt BDNF signaling by causing hippocampus neuronal atrophy. BDNF is an important growth factor that plays a role in neurodevelopment. BDNF and NR3C1 appear to interact in stress-related disorders, according to evidence (Braithwaite et al. 2015). In a study (Braithwaite et al. 2015), BDNF gene methylation changes in infants of pregnant women with depressive symptoms were examined, and it was reported that exposure to prenatal stress decreased BDNF methylation in infants. It is thought that this decrease in methylation in BDNF may reflect the molecular basis of conditions such as rapid maturation in the infant that can be induced by adverse prenatal events.

Additionally, animal models offer important opportunities to examine the relationship between early life stress and epigenetic changes. Maternal stress impacts HPA axis development and susceptibility in mice and rats, according to the research (Weinstock 2001, Kapoor and Matthews 2005). Weaver and colleagues (2004) examined the epigenetic effects of care of mother rats on baby rats and found significant differences in GR promoter methylation levels between high-care and low-care infant rat groups. Roth and colleagues (2009) examined the methylation levels in the BDNF gene, leaving the baby rats with caregivers who have harassing behavior to investigate the epigenetic effects of abuse at an early age and observed persistent changes in DNA methylation of the BDNF genes in the prefrontal cortices of maltreated rats in infancy. Moreover, changes in DNA methylation of the BDNF genes were observed in the offspring of maltreated female rats. The rats were separated from their mothers after birth in another study whose aim was to examine the effect of early life stress among generations.As a result, it's been observed that these rats exhibit depressive-like behaviors in adulthood, and that their behavior has changed in new and uncomfortable environments. It has been observed that these behavioral changes pass to the rats who are separated from their mothers and the next generations.

In another study (Franklin et al. 2010), which aimed to examine the intergenerational effects of early life stress, mice were exposed to maternal separation immediately after birth. These mice were found to exhibit depressive-like behaviors in adulthood, and their behavior changed in new and uncomfortable environments. Many of these behavioral changes have been found to be passed on to the offspring and next generation of separated mice. The methylation profiles of genes selected in relation to emotional or depressive behaviors have been examined in stress-exposed mice in generations 1 and 2. They have been shown to be a hereditary change in the regulation of DNA methylation in the germlines. The results showed that early life stress may cause permanent behavioral change and methylation profiles in certain genes may be inherited across generations. Thus, it has been observed that a behavioral and molecular correlation occurred. The topic of epigenetic inheritance will be examined in detail in the following parts of the review.

Epidemiological studies show that stress induced by environmental factors in early life is strongly associated with various behavioral changes, neurodevelopmental disorders such as hyperactivity disorder, schizophrenia, autism, depression, and post-traumatic stress disorder (Meyer et al. 2011, Brown 2012).

Post Traumatic Stress Disorder

According to the definition of post-traumatic stress disorder (PTSD), the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a person must have experienced or witnessed a highly threatening trauma to be diagnosed with PTSD. There are four symptomes observed in the person after this truma. These symptoms can be termed as recurrent distressing dreams, re-experiencing the event, the person's desire to avoid memories and conversations, and some cognitive-emotional changes. (Prakash ve ark. 2015, Maeng ve Milad, 2017, Bryant 2019). A key difference between PTSD and other mental health disorders is that PTSD has a clear starting point and a significant triggering process. Many events such as sexual abuse, traffic accidents, war, some diseases, especially cancer, and natural disasters are the causes of a wide variety of trauma. PTSD can get caused by a single traumatic situation or after exposure to long-term and continuous trauma (Bisson et al. 2015). Post traumatic symptoms usually occur within three months. However, there are some clinical cases where symptoms occur years later (Bryant 2019).

We know that only a small portion of people exposed to trauma are diagnosed with PTSD. The factors that cause a person to develop PTSD are classified as risk factors. Genetics, the lack of education, gender, age and the lack of living conditions in society are known to be an important factor in the formation of this disorder (Maeng and Milad 2017, Bryant 2019). Clinical studies to identify key genetic factors have shown that the genes involved in the emergence of PTSD are the ones associated with a number of psychological disorders. More than 50 genes

specifically involved in the function of the HPA axis have been determined to be associated with PTSD (Fischer et al. 2021). Many risk factors such as poor parental support, low socioeconomic situation, delay in diagnosis, and failure of treatment which we also have observed in many psychiatric disorders are also applicable to PTSD patients (Qi et al. 2016).

Post Traumatic Stress Disorder and Hypothalamic Pituitary Adrenal Axis Relationship

Occurrence of PTSD is related to biological disorders. In the case of PTSD, the regulation of the HPA, which is known to initiate the stress response, is disrupted. HPA is one of the main biological systems that work together with the immune system and respond to stressful situations. Glutamate has a significant role in HPA regulation. GABA as a main inhibitor of glutamate contributes to weakening and inhibiting the stress response. In a study of people with PTSD, high levels of glutamate and low levels of GABA were identified in blood samples (Murray and Holton 2021).

Cortisol has a important role in fear conditioning. Changes in the amount of cortisol, the final product of the HPA axis, are one of the focal points of post-traumatic stress disorder studies. Based on the results of some clinical studies, it has been observed that individuals with post-traumatic stress disorder have low cortisol levels. These results support the idea that individuals with PTSD are more sensitive to the cortisol effects of glucocorticoid receptors, and therefore the inhibition of the HPA axis is much higher than normal. In stress conditions, the increase in cortisol levels in the person causes this stress associated with the memory to be stored in the memory for a long time. Although there are inferences about the effects of high cortisol levels on PTSD, the issue is whether low cortisol levels have an impact on developing PTSD. In addition, polymorphisms in NR3C1 and FKBP5 genes known to have significant roles in the HPA axis regulation have an effect on people developing post-traumatic stress disorder. This is one of the scientific data that reveals the relationship between the HPA axis and PTSD (Carvalho ve ark. 2017, Fischer ve ark. 2021).

Post Traumatic Stress Disorder and Epigenetics

Epigenom can be altered by the effects of environmental factors as well as genetic factors. Animal experiments and post-clinical studies have shown that epigenetic changes begin in the uterus and continue throughout life. Studies were conducted on candidate genes and their epigenetic changes, especially on the HPA axis (Jiang et al. 2019). FKBP5, NR3C1, BDNF, BRSK1, LCN8, NFG, DOCK2, ZFP57 genes, are among the target genes in which epigenetic modification changes are detected in PTSD (Howie et al. 2019). DNA methylation is the most studied epigenetic modification in PTSD studies. In order to examine the differences in DNA methylation in individuals who develop post-traumatic stress disorder, studies have been carried out on many communities that have experienced major traumas (Mehta et al. 2019). Some studies of war veterans who developed post-traumatic stress disorder have shown changes in the methylation of their glucocorticoid receptor genes. Similarly, this methylation observed in the glucocorticoid receptor gene is considered to be related to parental trauma and hereditary risk profiles (Vukojevic et al. 2014). Studies conducted by Michels et al. (2013) have shown that changes in the methylation state of differentially methylated regions (DMR) are statistically more realistic and consistent. In a study (Krzyzewska et al. 2018), as a result of a study with a group of police officers with a trauma history, high methylation was detected each time in a DMR in the PAX8 gene, which encodes a transcription factor that contributes to the development of the thyroid and central nervous system. This suggested that looking at methylations in DMR regions may provide more different information on the relationship between PTSD and DNA methylation. In individuals who develop PTSD, differences in DNA methylation have generally been identified in genes responsible for immune function and inflammation. In the differentially methylated genes of patients who develop PTSD, 60% of them are the genes related to innate immunity. A recent study found significant differences in DNA methylation in patients who were abused as children and developed PTSD as a result, compared to patients who developed PTSD without a history of abuse. Recent reserch has revealed significant differences in DNA methylation in patients who were abused as children and developed PTSD as a result, compared to patients who developed PTSD without a history of abuse (Smith et al. 2011). As a result of the study by Katrinli et al. (2021), with a group with African-American trauma background, increased methylation was observed in two different DMR regions called HLA-DPB1 and SPATC1L, in the case of PTSD. Increased methylation in HLA-DPB1 supported the idea of the relationship between the immune system and PTSD. As a result of studies conducted with samples taken from people who developed post-traumatic stress disorder, changes in the transcriptional level of epigenetic markers were observed in some genes that may cause synaptic plasticity and long-term behavioral changes (Zovkic et al. 2013). At this point, the two genes studied extensively, one of which is the NR3C1 gene which encodes the glucocorticoid receptor where these epigenetic

changes are detected and the other of which is the FKBP5 genes involved in the activation of this receptor, have key roles in the regulation of the HPA axis (Chatzittofis A et al. 2021).

Studies have shown that the methylation seen in glucocorticoid receptors in particular has been effective in the development of PTSD. It was also concluded that the epigenetic changes seen in the FKBP5 gene and its glucocorticoid receptors, which plays a role in its activation, have important roles in creating a stress response and are directly related to the development of diseases that may occur following trauma (Robert ve ark. 2015). A study of African American children showed that the effect of the FKBP5 gene single-nucleotide polymorphism and childhood abuse impact on the development of PTSD depends on environmental influence. The study showed that those who were not abused and homozygotic for the T allele of rs9470080 have the lowest risk of developing PTSD whereas those who were abused and homozygotes have the highest risk.This study demonstrates that even thugh there is no genetic impact on the development of the disease, the interaction of gene and environment has important effects on PTSD (Digangi J ve ark. 2013). In one study conducted with samples taken from men and women who survived the Rwanda Genocide, DNA methylation at the NR3C1-1F promoter in men is conclude to be associated with the risk of developing post-traumatic stress disorder. Also, they suggest that this methylation has effects on traumatic memory. Hypermethylation has been detected in the NRC31 gene. It was thought that this situation was also related to prenatal stress and the stress exposed in the uterus. This proved the functional relevance of DNA methylation. In line with these data, it has been suggested that NR3C1 DNA methylation may serve as a marker for post-traumatic stress disorder (Vukojevic ve ark. 2014).

The brain-derived neurotrophic factor (BDNF) is a type of neurotrophin with higher concentrations in the prefrontal and hippocampus regions of the brain. Levels of BDNF have been identified to decrease in certain neurodegenerative and psychological disorders. In some studies, it has been shown that there are changes in the amount of BDNF in some dementia conditions such as Alzheimer's, Bipolar Disorder, Huntington's Disease.Therefore, it is thought that the change in the amount of BDNF may have an effect on the formation of these disorders. There are many opinions that this is because of the fact that the BDNF is the initiator of biochemical changes that will lead regulation of synaptic plasticity in many brain regions (Brigadski et al. 2014).

It is known that there is a decrease in BDNF expression in the hippocampus as a result of stress caused by a traumatic situation that triggers some psychological disorders such as PTSD. Along with this reducing effect on BDNF expression, distortions in both prefrontal cortex and neural plasticity were observed. It has been seen that changes in plasticity affect the emergence of post-traumatic stress disorder (Claudino et al. 2020). Researches have been conducted on the mechanisms responsible for the alteration of BDNF gene expression based on the trauma situation. Researchers determined that the H3K9me2/3 epigenetic mark, which lowers the BDNF gene protein levels by binding to the promoter regions in this gene, changes under stress conditions. Studies with rats exposed to unavoidable foot shock have determined that BDNF gene expression is decreased by the effect of H3K9me2/3 epigenetic mark increase. This suggested that H3K9me2/3 has an effect on the emergence of post-traumatic stress disorder (Zhao et al. 2020). In some animal experiments, they determined BDNF mRNA down-regulations in rats that exhibited PTSD-like responses after trauma. In addition, changes in histone acetylation of BDNF promoters were detected in rats exposed to long-term stress. There are also a number of studies showing that the genetic target for PTSD is the BDNF gene in the hippocampus (Takei et al. 2011).

Three common histone modifications which are histone methylation, histone phosphorylation, and histone acetylation, are the major epigenetic modifications that influence the emergence of post-traumatic stress disorder (Howie et al. 2019). Histon regulations are included in activities associated with emotional changes in PTSD processes, especially in the encoding of traumatic memory (Howie et al. 2019). Posttraumatic stress disorders are directly related to the disruption of the fear memory retrieving process.

Clinical studies aimed to highlight the mechanism behind the emergence of PTSD have focused intensely on neuroepigenetic mechanisms. Studies on human beings are limited to peripheral tissue and cannot provide too much information at this point. Therefore, studies with experimental animals constitute the majority of the literature on these neuroepigenetic mechanisms. PTSD studies conducted in rodents have shown that these neuroepigenetic modifications are effective in the emergence of post-traumatic stress disorder in two different ways: fear memory disorder and stress response (Kim et al. 2018). Histone acetylations are associated with activations during transcription. Studies related to histone acetylation have mostly been studied in the context of memory and learning. In experiments, an increase in acetylation was detected the same as in phosphorylation of the hippocampus CA1 region and the lateral amygdala H3 histone in the case of fear memory recovery (Kim et al. 2018). Histone acetylation is thought to be associated with a reduction of conditioned fear responses. In studies with mice without enzymatic avtivity of histone acetyltransferase, impaired memory functions were

observed and the role of histone acetylation in the memory function of the brain was proven (Bahari-Javan et al. 2014).

Epigenetic Inheritance

Identical twins have almost the same genome and unrecognizable similar epigenetic markings when they are born. Although, their environment and the environmental effects they experience will cause this epigenetic information to change over time. This results in individuals having different phenotypic features. These differences in identical twins are one of the strongest proofs of epigenetics's huge role in phenotype which is changing due to environmental changes (Fraga et al. 2005). For a long time, the scientific world has focused on DNA as a material for the genetic process. But with some studies which change their focus on environmental effects, they come to the conclusion that the just DNA has not been sufficient to explain the inheritance. Although this is seen as a result of genetic and environmental factors, epigenetic inheritance combines these two independent factors (Daxinger ve Whitelaw 2012).

Epigenetic inheritance can be defined as the transfer of exposure to genetic changes, which is the result of epigenetic modifications, to the next generation without any change in the DNA sequence (Sarkies 2020). Research has shown that both temporary and long-term environmental impacts cause permanent changes in epigenetics. The idea that epigenetic regulations do not only reflect cell history as a result of the different disturbance conditions observed but also provide mechanisms that could affect the response of the person and even his future generations to future events has become more evident. As a result of the different disturbance conditions observed, the idea that epigenetic arrangements do not only reflect the cell history, but also offer mechanisms that can affect the reactions of the person and even his future generations to future events has gained strength.

Different methods such as insufficient maternal care and fear conditioning are some of the methods used in animal studies. The studies show that long-term epigenetic changes have been observed in the HPA axis as a result of early stress in mammalian experimental animals. On the other hand, some stress conditions have resulted in an epigenetic change in experimental animals which later caused drug addiction development (Bohacek ve Mansuy 2013). The F0 mothers subjected to pre-pregnancy stress showed inadequate maternal care in F1 generations and inheritance of depression-like behavior in F2 generations. Therefore, some changes have been detected in the TOR-Akt signal path. In addition, clinical trials have shown that, as in animals, parental relationships are very important in people. Also, it has shown that there may be some personality disorders in the absence of these. Certainly, the increase in sensitivity to the post-traumatic stress disorder of the children of people who survived the Holocaust and Rwanda Genocide and the increased rates of depression, anxiety, and in number of diseases, is the greatest evidence of the epigenetic inheritance of trauma for future generations (Jawaid 2018).

It has been accepted that epigenetic modifications caused by environmental impacts are transferred not only to those exposed to environmental impact but also to subsequent generations. As a result, these epigenetic changes in individuals, on the basis of epigenetics, are categorized in two different group. As a result of recent studies, epigenetics which includes short or long-term epigenetic changes that occur in an individual their entire life grouped as “direct epigenetics”. There are numerous examples that can be attributed to direct epigenetic changes. Many environmental factors such as smoking, environmental pollution, and poor living conditions can cause changes in the epigenetic mechanisms of the person which will contribute to the development of diseases such as cancer, autoimmune diseases, anxiety and depression. Many studies have shown that epigenetic changes are a serious risk factor for the occurence and progression of psychological disorders. Some animal studies showed that the quality of maternal care has a significant impact on changing the child's epigenetic mechanisms (Lacal ve Ventura 2018). Epigenetic changes that may cause changes in the phenotypes of future generations by transferring the epigenetic changes that occur in the generation that has a direct experience. This type of inheritance is examined under “indirect epigenetics”. Animal experiments in the field of indirect epigenetics are designed to examine the implications of the indirect effect of environmental factors exposed during pregnancy on offspring development.In one study, permanent DNA methylation changes were detected in the sperm of the offspring of mice exposed to prenatal malnutrition. In addition, there are also some study findings showing that susceptibility to depression in offspring is directly related to the activation of the mother's immune system. There are examples where this indirect inheritance occurs through both paternal and maternal (Kürekçi ve ark. 2017, Lacal ve Ventura 2018).

Two Different Scenarios: Intergenerational and Transgenerational Inheritance

Today, many psychological disorders are thought to have a hereditary component. Therefore, it is particularly important to understand and define properly epigenetic inheritance. The importance of epigenetic mechanisms in the transmission of disease risk across generations has been ignored for a long time because it is incompatible with the Mendelian model of inheritance. For a long time, it has been accepted that the transfer of past experiences to the future is possible only with genes and maternal care. However, as a result of studies which show that epigenetic changes can be hereditary, it has begun to be mentioned about epigenetic inheritance that occurs with the participation of environmental effects and genetic factors (Bohacek ve Mansuy 2013). As a result of many studies, it has been concluded that the effects of epigenetic inheritance can be in two different ways as intergenerational and transgenerational. The main difference that enables this distinction is about in which generations the inheritance is observed. Intergenerational inheritance is when the epigenetic changes that occur and are preserved in the F0 individual are transferred to the next F1 generation, but if these epigenetic modifications are not inherited in the F2 offspring due to the reprogramming that takes place in the germline although they are preserved in the somatic cells. To summarize, when the effect of the change in the mother or the father is observed in their children, this is categorized as intergenerational inheritance. If the epigenetic change motifs from F0 are observed in F2 or F3 generations as a result of escape from preimplantation even when environmental effects are removed, then we can mention transgenerational inheritance (Kürekçi et al. 2017, Horsthemke 2018).

Intergenerational and transgenerational effects can occur as both deleterious mutations and adaptive mutations. The majority of experiments designed for intergenerational and transgenerational inheritance is done with rodents. Morover, there are many clinical studies proving that traumatic stress is inherited both transgenerationally and intergenerationally (Burton ve Greer 2021). Intergenerational inheritance has been demonstrated by clinical studies in which certain behavioral disorders and depression symptoms were detected in children from families who were forced to migrate. In addition, there are data showing that the intensities of parental exposure to war trauma and various psychological disorders are directly proportional in the next generations of Vietnam War, the Second World War and the Bosnia and Herzegovina War survivors (Jawaid ve ark. 2018).

One of the biggest evidence of transgenerational development is the genomic printing process. Genomic imprinting is a process in which genes are expressed by just one of the two alleles that are inherited from parents in the developmental process. At this stage, the other parental allele is silenced by epigenetic mechanisms. Traits of the parent to which both the silenced allele and the expressed active allele belong are protected for generations. A delusion in a chromosome can result in two different phenotypes, depending on whether it is caused by maternal or paternal origin. Epigenetic reprogramming of the embryo in the preimplantation stage occurs selectively. Features which are inherited from the parents are allowed to be inherited by the new embryo due to this selectice process (McGrath ve Solter 1984, Bošković ve Rando 2018). Due to emergence of transgenerational inheritance and decay of Mendelian Inheritance model at this point, the causes of many neuropsychological and immunological disorders that could not be explained in the previous process have been understood.Especially in studies conducted with the grandchildren of individuals who survived the Holocaust Concentration Camp and the Dutch Hunger these individuals have been identified as having a potential for disease (Fernandez-Twinn ve ark. 2015). One study performed with mice showed glucose dysregulation up to the next fourth generation and depressive-like behavior up to the third generation as a result of exposure to traumatic stress in the early postnatal period (Steenwyk ve ark. 2018).

Maternal and Paternal Influence in Epigenetic Inheritance

Many recent studies have revealed that intergenerational inheritance can be both maternal and paternal. Rodent studies have shown that exposing the mother to stress during pregnancy and the father during mating causes molecular changes that alter the offspring's susceptibility to stress (Lacal ve Ventura 2018). Fetal programming process is the most important process to be understood in order to fully resolve the effects of maternal and paternal inheritance.

Fetal programming is a process that includes epigenetic changes that triggers the molecular development of the fetus. At this stage, epigenetic changes can occur as characteristics expressed by the offspring after birth (Kanherkar et al. 2014). The effects of prenatal stress on the fetal brain development of the offspring, epigenetic signs associated with neurological diseases, and the observation of the effects of maternal nutrition on the offspring physiology are some of the examples which are included in the fetal programming. Additionally,

epigenetic changes has been determined in the adolescent period cortisol receptor genes in the children of women exposed to domestic violence.

The most important feature of the maternal-induced stress situation is that the stress exposed in the uterus can affect the germinal cells of the female fetus. The most important feature of the maternal-induced stress condition is that the stress exposed in the uterus can affect the germinal cells of the female fetus. This has the potential to transfer these hereditary epigenetic changes to future generations. Causes of prenatal stress can be physiological or psychological violence that the mother is exposed to during pregnancy. Therefore, the stressful situation during pregnancy can seriously affect the infant's development (Bohacek and Mansuy 2013). However, the changes in the future individual do not have to be caused only by intra-uterine stress exposure or immortality in postpartum behavior. Likewise, there are some data which illustrates that epigenetic changes in parent germ cells can be transferred to daughter cells by fertilization (Kanherkar et al. 2014).

Epigenetic changes from paternal origin transmitted to the offspring are as important as those from maternal origin. Although there is not much research for the process through sperm, there have been some behavioral and biological differences in future generations as a result of epigenetic changes triggered by environmental factors such as excessive alcohol use, smoking, and stress (Bohacek ve Mansuy 2013). Some studies have shown that paternal or grandparent malnutrition has effects on the phenotypes of the next generations. This has been shown to increase the risk of developing diabetes and heart disease among grandchildren (Lehrner and Yehuda 2018). There are also some clinical studies showing that sperm DNA methylation is affected by fathers with excessive alcohol use (Curley et al. 2011).

The experiences of the father may cause molecular changes via sperm, which will cause some cognitive processes to be disturbed, especially affecting the HPA axis, especially through sperm. In mammals, it has been found that an epigenetic change in paternal germ cells has been strongly seen in the F1 generations, but in F2 and F3 generations permanent phenotypes are less found (Bošković ve Rando 2018). In other words, the form of the inheritance seen in this F1 corresponds to intergenerational inheritance. When the pregnant female is exposed to stress, both the fetus and the fetal germline can be affected by this stress. That's because the female oogenesis process started while she was in the uterus. In a situation of paternal stress, the germ cells of this individual can be affected as the father is exposed to stress, and epigenetic changes that will be caused by this stress can be transferred to his F1 offspring as a result of fertilization.

However, these cells are not affected by stress because spermatogenesis, which is the F1 offsprings germ cells formation process, began to create sperms during adolescence. Therefore, the chance of the heredity being seen in the F2 offsprings where the stress situation is eliminated will be less probable. If these ancestral epigenetic modifications are seen in F2 offspring, this type of inheritance can be called as transgenerational inheritance (Heard and Martienssen 2014, van Otterdijk and Michels 2016).

Conclusion

Psychosocial stress factors activate the response of the HPA axis in the body and cause increased glucocorticoid production (Harris and Seckl 2011). During development, social difficulties may cause disruptions in the HPA function (Spencer 2017). Studies show that defects in HPA function or regulation alter the methylation profiles of certain genes. In this review article, we have included many studies examining the relationship between early life stress and the methylation profiles of HPA axis-related genes such as NR3C1, CRH, CRHBP and FK506. An individual's exposure to psychosocial stress, mainly in early life, may lead to various epigenetic changes. Epigenetic mechanisms that are sensitive to environmental influences in early developmental stages may result in different phenotypic effects under stress conditions. Epidemiological studies show that stress induced by environmental factors in early life develops various neurodevelopmental disorders, such as post-traumatic stress disorder (Meyer et al. 2011, Brown 2012). In the case of PTSD, epigenetic approaches are very beneficial in considering the relationship between environmental factors and genetics. Therefore, we decided to include PTSD as a neurodevelopmental disorder in our review. It has been found that these changes have an effect on biological and behavioral characteristics such as synaptic plasticity and long-term behavioral changes. It is also known that PTSD results in a degradation of the regulation of the HPA axis. Epigenetic changes in genes that participate in HPA axis function, especially NR3C1 and FKBP5 genes, which are used as epigenetic markers, provide information about the effects of trauma on individuals and future generations.

After studies conducted with people who have experienced traumatic events such as war, famine, and natural disasters, similarities have been identified in epigenetic signs that may increase their susceptibility to many psychological disorders, especially PTSD, in those generations. These data are also supported by animal

experiments. Epigenetic mechanisms have emerged as the vectors of this inheritance pattern and many cases that Mendelian Inheritance is insufficient to explain have begun to be explained by epigenetic inheritance (van Otterdijk and Michels 2016). The better understanding of these psychological disorders and earlier intervention depends on obtaining more information about epigenetic inheritance mechanisms. The inheritance mentioned at this point can be both maternal and paternal.

Social epigenetics is a relatively new field, and studies in this field are insufficient in many aspects. One of the main reasons for this situation is that there are many experimental limitations. The involvement of multiple stressors when investigating psychosocial stressors makes examining the epigenetic effects of psychosocial stressors difficult. When it comes to investigating the epigenetic effects of a stress factor, the fact that the individual has been exposed to different stressors can create statistical confusion. Therefore, attention should be paid to the stress factors to be examined (Mulligan 2016). At the same time, researchers face the problem of tissue specificity when collecting biological samples, as there are situations such as tissue differences and cell differences within the same tissue. For this reason, it may be necessary to conduct long-term studies with patients in clinical trials (Waterland and Michels 2007).

Unexplained points and complexities in epigenetic mechanisms also complicate social epigenetics research. However, social epigenetics is a multidisciplinary field. In order to advance the work in this area, researchers from different fields, such as sociologists, biologists, and epidemiologists, should work together with a broad perspective. One of the limitations of studies associated with PTSD is that studies in humans are limited to peripheral tissues. Therefore, animal models are used to predict epigenetic changes in the brain.

However, the effects that occur in humans can be interpreted in a limited way on these animal models. Therefore, the need for new approaches is inevitable. PTSD studies have generally focused on DNA methylation. However, different histone modifications and non-coding RNAs are also quite remarkable in this process. Therefore, more studies about other modifications is a necessity. On the other side, studies on epigenetic inheritance are quite new. Information on transgenerational inheritance is also very limited. For this reason, there is a need for more sensitive techniques that scan the entire genome. Furhermore, the subject of sperm studies as a heredity factor and the hereditary effects of RNAs in the sperm has become very popular recently (Bohacek and Mansuy 2013). However, in order to carry out further studies, the tracking and characterization of RNAs in sperm next-generation sequencing is essential. Further studies in the field of epigenetic inheritance need to elucidate the mechanisms responsible for the transmission of information from the brain to the gametes. This may help develop new approches to prevent the transmission of epigenetic changes that cause different diseases in future generations (Klengel et al. 2016).

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Authors Contributions: The author(s) have declared that they have made a significant scientific contribution to the study and have assisted in the preparation or revision of the manuscript

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared.

Financial Disclosure: No financial support was declared for this study.