



The Era of Epigenetics: Therapy Influencing Gene Expression

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Editorial

The knowledge of epigenetical mechanisms significantly enlightens the dilemma 'nature or nurture' and constitutes a very important component for the outcome of psychiatric treatment and psychotherapeutic relationship with patients or clients who report traumatic memories and had experienced negligence or maltreatment.

The story starts from the beginning in the early 19th Century, when Lamarck argued that organisms can acquire characteristics and properties through their interaction and adaptation to the environment [1]. These new 'personality traits' can become lifelong stable and can be hereditated by the next generation [2]. The term 'epigenetics' which derived from Greek, was given to this organismic property. It means "above genetics".

There are two main mechanisms involved in epigenetics: DNA methylation and histone modification. A third mechanism concerning non coding RNA (ncRNA) needs to be more elucidated [3].

DNA methylation occurs when one methylgroup (CH₃) is added on the aminoacid cytosine. This is completed through the action of a methyltransferase only when cytosine is followed by guanine, and results in long term silencing of the expression of the specific gene. It is important to note that gene methylation is a multi-step procedure, while demethylation is performed through one single step [4].

These facts are highly important for the personality changes during psychotherapeutic interventions and psychiatry, since they show very high potential and flexibility on the multitude of lived experiences and they have a determining role in neuroplastic functions like learning, memorising and adaptive behaviour.

The second mechanism concerns histone modification. Histones are proteins positively charged. Unused DNA which remains unneeded carries a negative charge and, through attraction, it is packaged around an octamer of histones [2]. Histone molecules are subjected to methylation, acetylation or phosphorylation and can repress the genes expression by increasing the electrostatic load and tightening the coils, thus silencing DNA expression. Histone modification is transient resulting in less permanent changes than DNA methylation.

The agouti mice example shows the epigenetic changes that can be observed through gene methylation without DNA modification. The mouse with a methylated gene for hair and weight has dark gray hair and is underweighted in comparison to the mouse with non-methylated gene which is yellow and normal weighted [5].

As far as the research on Diabetes Mellitus type 2 is concerned, Dayeh et al. [6] found about 17 genes that seem to be differentially methylated in the pancreatic islets, thus contributing to decreased insulin release after glucose stimulation. Two years later, the same research team reduced the number of implicated genes to four [7].

Another brilliant example of epigenetic changes is the increased methylation of the gene which controls the production of the Brain Derived Neurotrophic Factor (BDNF) in stressful environments. BDNF has a crucial role in the creation of new synapses. The reduction of BDNF production results in a decreased number of new synapses and reduced symbolisation of experiences, thus diminishing the ability to memorise and learn [8,9].

In mice, stressful early life results in higher responses of corticosterone, which is the equivalent of cortisol in mice, and reduced neurogenesis in hippocampus during their adulthood. This methylation marker remains stable during life and is inherited to the next generation [2,10]. So silencing of the BDNF gene, combined with the down regulation on the BDNF transcription levels are a good indicator of early life stress and abusive childhood.

BDNF levels reduction in traumatic childhood may also have a teleological meaning, i.e., like a natural protection, so as to reduce accurate symbolisation of painful memories and support emotional survival. On the other hand, traumatic childhood increases stress in order to serve the need for hypervigilance, since the world can be perceived as a potential enemy, or even as a minefield.

McGowan et al. [11] studied the brains of suicidal children and found hypermethylation of the ribosomal RNA in the region 5' at the hippocampal area which controls the hypothalamo-pituitary-adrenal (HPA) axis. The outcome of this hypermethylation was abnormal regulation of the response to stress and suicidal tendency. In addition, Bustamante et al. [12] found a direct relationship between the increased cytosine-phosphate-guanine DNA methylation, childhood maltreatment and Major Depressive Disorder (MDD).

Oxytocin calms amygdala through reinforcement of the adducting fibers of GABA [13]. In order to have this outcome the BDNF production needs to be increased through demethylation of the BDNF gene. Psychotherapy or relaxation or even an appropriate environment will result in this gene demethylation as will be described below.

Empathic listening increases symbolization and reduces amygdala firing through activation of its middle and basolateral nucleus [14]. Uzefovsky et al. [15] studied the neurogenetic path of empathy in 367 participants and showed its close relationship with the oxytocin and arginin-vasopressin related genes. Schneiderman et al. [16] found a direct relationship of oxytocin secretion with the reciprocity of the partners, their positive regard, their tender touch and their caring for the relationship. They concluded that this situation has many similarities with the mother-infant relationship and the primary attachment. Lutz et al. [17] assert that empathy and compassion create an environment for a higher integration degree of our nervous system.

Yoga-although it is not therapy-contributes to relaxation and insight. One controlled study showed a significant increase of oxytocin in fifteen schizophrenic patients after a month of yoga exercise [18].

It would be of interest to study the degrees of methylation of

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oxytocin and of BDNF gene and their relationship with empathic understanding, in order to understand the exact path to higher neurogenesis and synaptic activity. Studies examining demethylation of the oxytocin gene after couple therapy would be mostly interesting, for the neuroscience of romantic relationships.

Concerning the pharmacology progress in this field, Lopez et al. [19] showed a decrease of methylation of the BDNF gene in the prefrontal cortex after an eight week therapy with citalopram. Clinical signs of depression were also improved. They proposed that the methylation demethylation procedure is a dynamic process which is included in the substrate of cognitive changes during therapy.

Methyltransferase and histone deacetylase inhibitors are, at present, the main target for preparation of epigenetic drugs which will be used in mental disorders [20] and have already shown interesting results.

From the perspective of Psychotherapy, Perroud et al. [21] studied the changes of DNA methylation in the plasma BDNF in 115 patients with bipolar disorder and 52 controls during intensive four-week process with *DBT* [22]. They found significant BDNF methylation decrease which was followed by significant changes in the scores of depression, despair and extroversion-spontaneity. They added that the higher the trauma degree, the higher the BDNF methylation and gene silencing was.

Yehuda et al. [23] studied the epigenetic biomarkers NR3C1 and FKBP5 which are glucocorticoid receptor related genes, as predictors of the therapeutic outcome and indicators of improvement, in fifteen combat veterans with PTSD, who underwent a twelve weeks prolonged exposure in psychotherapy. They found that NR3C1 methylation level could significantly predict the therapeutic outcome while the FKBP5 methylation showed a congruent result with the improvement of symptoms suggesting increased gene expression. Moreover, the increased sensitivity of the glucocorticoid receptor, which as they state is a hallmark of PTSD showed a lower expression after therapy.

Arthur Weidman [24] notes that, when parenthood and psychotherapy are focused on the primary attachment, then they can be significant tools for demethylation of important genes. Kohut [25] advocated that humans have an innate tendency which can be sidetracked by non-empathic behaviour of parents, thus approaching to the humanistic attitude of actualizing tendency and the reactions of defense described by Rogers in his theory of personality [26].

Change of attitudes and personality development can happen also through the relationship with good partners or friends. However, psychotherapy is probably the second after parenthood most powerful process that humans dispose, in order to alterate their beliefs thus relieving the psychic pain. Psychotherapy helps to reduce the hyper-reactivity of the HPA axis through an experiential enrichment of emotions, beliefs and behaviours. The therapeutic process aids and supports humans to discover their wide range of organismic traits, change their genes expression and develop more skills in order to actualise their life goals [26].

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