



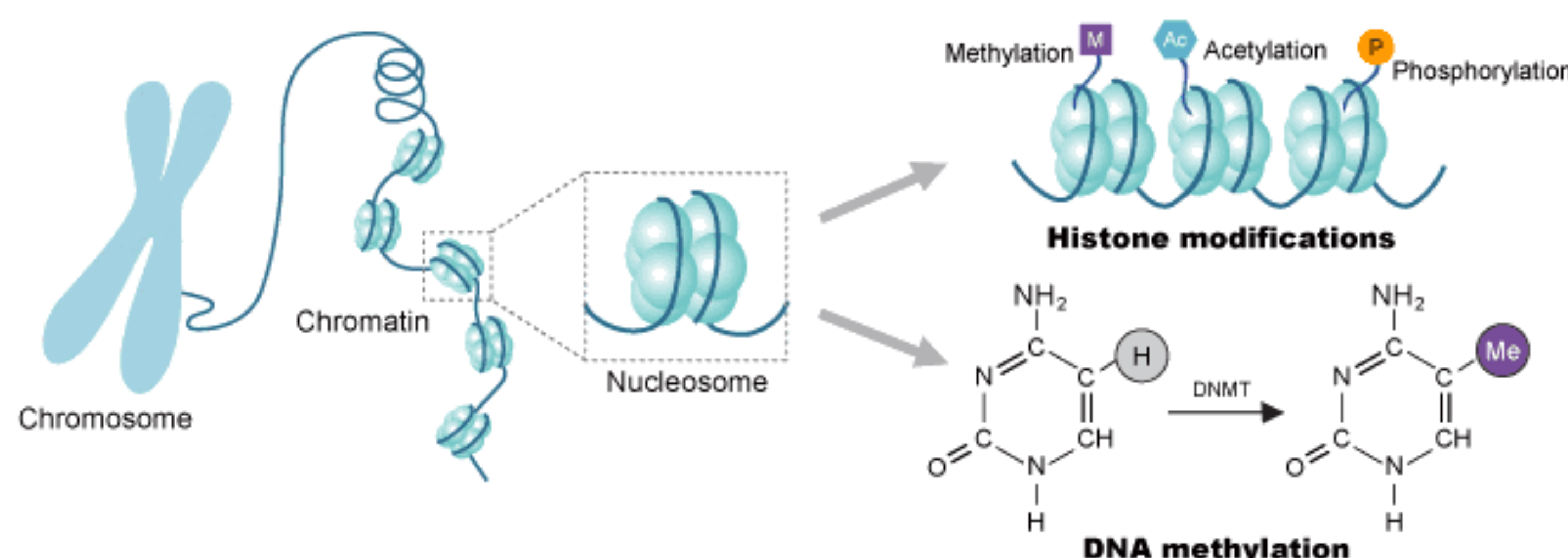
Effective Reversal of Epigenetic Alterations

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Introduction

Epigenetics is the study of changes in gene function that are heritable and that are not attributed to alterations of the DNA sequence. These alterations are due to either DNA methylation or histone modification, which leads to variations in how that gene is expressed by the body. Traumatic events are connected to epigenetic alterations, where they can predispose trauma or appear as its result. Effectively treating trauma involves the reversal of these epigenetic modifications, either through direct or indirect means. Direct means include pharmacological therapies, whereas indirect means involve behavioral therapies that alter epigenetics as a byproduct. The main question addressed was: what method is most effective at reversing the effects of epigenetic modification, pharmacological therapy or behavioral therapy?



Background

-Alterations can occur through alteration of charges on the DNA, DNA methylation, RNA associated silencing, histone modification, or ATP-dependent chromatin remodeling complexes.

-each function to alter the expression of certain genes, turning them “on” or “off”.

-Trauma: psychological and emotional response to an event or experience that is deeply disturbing or distressing.

-Research has found that 70% of adults have experienced trauma in their life.

-Post Traumatic Stress Disorder is estimated to be 30-70% heritable.

-Trauma and epigenetics: related through their impact on the body

-trauma alters methylation of several gene promoters which change gene expression

-epigenetically alters the DNA of the experienter and their offspring

ex) studies have found that survivors of the Holocaust raised anxious children who had epigenetic tags associated with the trauma of their parents.

-In understanding that epigenetic alterations occur on top of the DNA (rather than changing the DNA sequence itself), it becomes clear that effective treatment must involve the removal of these tags

Direct Treatment: Pharmacological Intervention

Methionine Infusion:

- Reverses methylation caused by low-grooming mothers in rat pups

Histone Deacetylase Inhibitors

- Activates chromatin that eliminates effect of poor maternal care in rat pups

Zebularine treatment

- DNA methylation inhibitor that reverses methylation of protein which promotes nerve cell growth and maturation

Synthetic Transcription Factor

- Reactivate genes silenced through epigenetic modifications by interacting with chromatin, altering cell back to normal

Indirect Treatment: Behavioral Therapy

Exposure Therapy

- Safe presentation of anxiety trigger
- Decreased methylation of FKBP5 gene (which is associated with depression)

Mindfulness Based Stress Reduction (MBSR)

- Meditative approach that combines mindfulness with yoga
- Decreased methylation of FKBP5 gene
- Reduces histone deacetylase

Reconsolidation Update

- Targeting negative memory as person recalls it in order to alter thoughts around it
- Phosphorylates glutamate 1 receptors in the amygdala, removing them

Analysis

Pharmacological Intervention

- Reverse effects of epigenetic alterations on DNA back to pre-trauma state
- Little research on human subjects
- Eradicate physiological cause of anxiety/depression without treating the mental or emotional burdens—increased chance of relapse

Behavioral Therapies

- Treat the psychological underpinnings of trauma, which reverses epigenetic alteration as a byproduct
- Reconsolidation update functions best in a narrow window following exposure, limiting its effectiveness
- Mindfulness based stress reduction functions even after significant time has passed

Conclusion

Mindfulness Based Stress Reduction is the safest and most effective option

- No side effects that are associated with drug use
- Can treat trauma long after exposure
- Treats both the psychological and physiological consequences of trauma

Much research is left to be done in both fields of treatment, and in the field of epigenetics as a whole

Bibliography

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Publisher.

Bishop, J.R., et al. (2018, September 18). Methylation of FKBP5 and SLC6A4 in Relation to Treatment Response to Mindfulness Based Stress Reduction for Posttraumatic Stress Disorder. *Frontier Psychiatry*. DOI: 10.3389/fpsy.2018.00418

Felsenfeld G. (2014). A brief history of epigenetics. *Cold Spring Harbor perspectives in biology*, 6(1), a018200. <https://doi.org/10.1101/cshperspect.a018200>

Haynes, K., Silver, P. (2011, June 12). Synthetic Reversal of Epigenetic Silencing. *The Journal of Biological Chemistry* VOL. 286, NO. 31, pp. 27176 –27182. <https://www.jbc.org/content/286/31/27176.full.pdf>

Kaliman, P., et al. (2014, February) Rapid changes in histone deacetylases and inflammatory gene expression in expert mediators. *Psychoneuroendocrinology*. 40: 96–107. 0.1016/j.psyneuen.2013.11.004

National Council for Behavioral Health. (2011). How to Manage Trauma infographic. [Infographic about trauma statistics and management.]. Retrieved October 10, 2020, from <https://www.thenationalcouncil.org/wp-content/uploads/2013/05/Trauma-infographic.pdf?daf=375ateTbd56>

Trauma-informed care in behavioral health services. (2014). Rockville, MD: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment.

Yehuda, R., et al. (2013, September 27). Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Frontier Psychiatry*. <https://doi.org/10.3389/fpsy.2013.00118>