Stress, psychiatric disorders, the epigenetic causes and possible treatment pathways

Introduction

Epigenetics has revealed how factors in your environment affect how genes are expressed, which extends to all the systems in our body. This provides a framework for understanding the pathways of effects (and possible treatment) of adverse environmental effects which may otherwise be irreversible. Current epigenetic studies describe how chronic stress, or abnormal early life stress may leave permanent changes on the brain, leading to a variety of psychiatric disorders. Looking at the underlying epigenetic chain of events, we may be able to prevent or reverse these effects through pharmacological treatment.

Epigenetics explores how sections of our genome can be added to, to give way to additional changes. This means that the effects of certain genes might be exacerbated or repressed. Moore (2017) outlines the two most currently studied and understood epigenetic mechanisms; DNA *methylation is* when chemicals called methyl groups attach themselves to the backbone of our DNA; and the second method is *acetylation* and *de-acetylation*, involving acetyl groups. Moore (2017) then explains how this additional group of chemicals either dampens (methyl groups) or strengthens (most acetyl groups) the effect of the gene on its related functions such as protein production. When something like a gene referred to as the *Brain-Derived Neurotrophic Factor* (BDNF) becomes methylated, the gene becomes *downregulated* meaning the functions (neurotrophin production) are less prevalent.

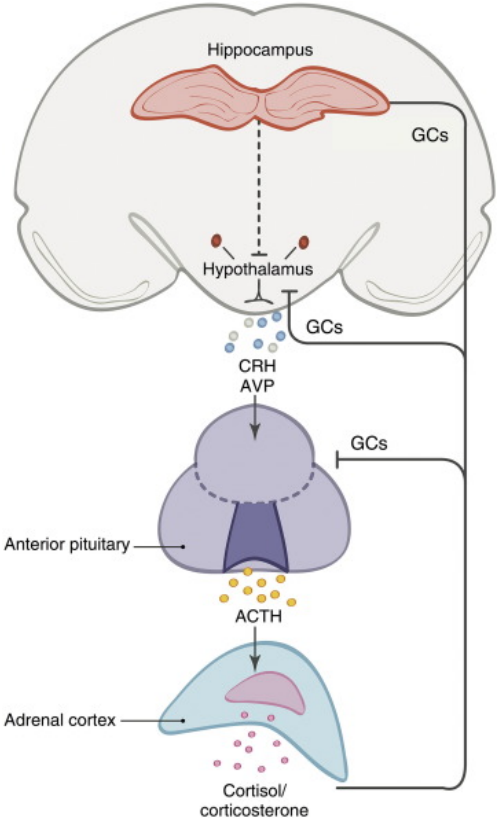
The effect of this downregulation of BDNF has been strongly linked to both psychiatric illnesses and stress by Naert et al. (2011). This may due to the disruption of the stress regulatory system named the *hypothalamus-pituitary-adrenal (HPA) axis* (Lee and sawa 2014). The HPA-axis is a major neuroendocrine system which could influence many other systems if it were dysfunctional. The two main treatments reviewed (Perla et al. 2014 and Roth et al. 2009) focus on how to re-normalise a dysregulated HPA-axis, and reverting BDNF suppression respectively.

The stress pipeline

The *hypothalamus-pituitary-adrenal* (HPA) axis is the key system linked with our body's management of stress. It is constantly releasing and neutralising glucocorticoids (stress hormones) which influence the signalling of other systems. Abnormal stress increases the regular glucocorticoid levels, which several studies have found may shape HPA-axis development i.e. modify the genes related to the HPA-axis (Naert et al. 2011).

The current model of how this occurs is outlined by Argentieri et al. (2017). Stress in the brain triggers the release of a corticotropin releasing hormone (CRH) in Figure 1 by the hypothalamus. The purpose of CRH is to bind to the receptors CRH-R1 and CRH-R2, which causes the pituitary gland to secrete another hormone called ACTH. It travels the bloodstream and, like CRH, binds to its respective ACTH-R receptor. Finally this causes the adrenal cortex to produce glucocorticoids such as cortisol. These glucocorticoids (GCs) travel to many areas of our body, most notably the brain and feedback into the HPA-axis.

Figure 1



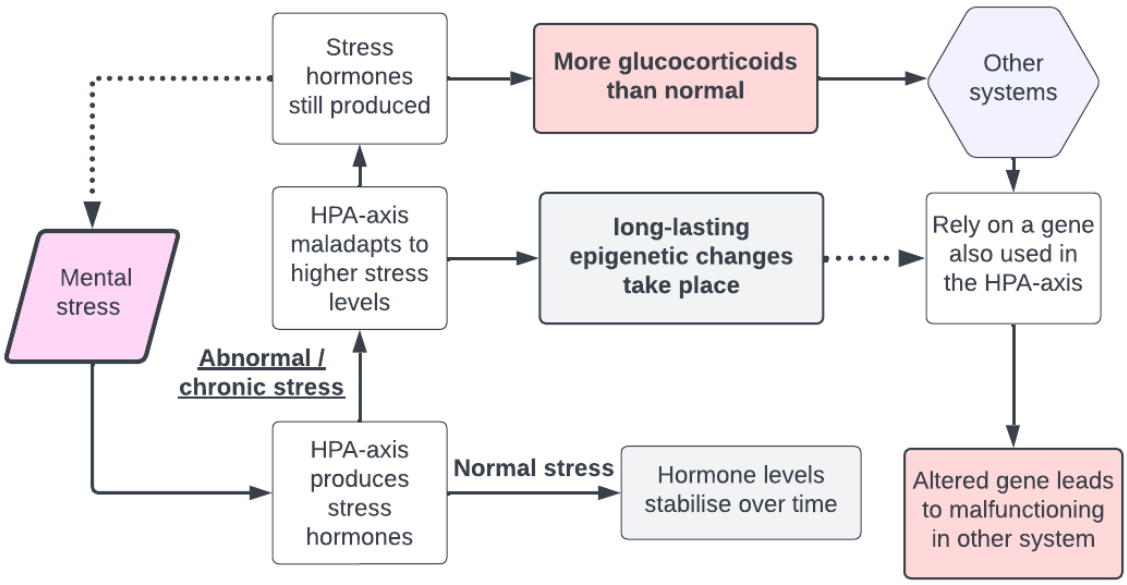
Overview of the hypothalamus-pituitary-adrenal (HPA) axis: biochemical feedback pathways. Reprinted from Argentieri et al. Copyright 2017 by Elsevier. Permission not required for non-commercial use.

Argentieri et al. (2017) also justifies how glucocorticoids are important due to their role in controlling metabolism and inflammatory responses in tissue, they bind and modify the glucocorticoid response elements (GREs) in DNA. Depending on how the GREs are modified, immune, inflammatory and metabolic proteins may then be produced more, less or not at all. They have been measured to influence many other processes alongside the methylation of genes (Chatzittofis et. al 2021). Thus as seen in Figure 2, the HPA-axis's stress hormones exert influence over a variety of key bodily systems such as the nervous, cardiovascular and immune systems. Lee and Sawa (2014) and Argentieri et al. (2017) and many others explore the effects the

HPA-axis has on a variety of psychiatric disorders alongside Roth et al. 2009's rat experiments.

Maladaption of genes in the HPA-axis expresses itself through abnormal baseline cortisol levels - Lee and sawa (2014) and Figure 2 outline how this recurs and thus further dysregulates the HPA-axis. An issue with this is that genes associated with the HPA-axis are (much like glucocorticoids) associated with many other important bodily systems (Chatzittofis et al. 2021). One key gene that is anticipated to be affected by HPA-axis dysregulation is the aforementioned BDNF.

Figure 2



How adverse stress leaves long-lasting effects on the HPA-axis and other physiological systems (no citation needed)

BDNF, or *Brain-Derived Neurotrophic Factor* is a gene section associated with the HPA-axis but also much of the brain (Naert et al. 2011). Miranda et al. (2019) delve into the fundamental role of BDNF in memory, both normal and abnormal. They explore many studies which show BDNF regulates the neuroplasticity of our brain, an essential part of how memories work. An increase in BDNF has been shown to increase neurogenesis, meaning that there are more neurons formed and thus more learning and memory capabilities.

This implies that a decrease in BDNF is unhealthy, and could lead to memory detriment. The likely conclusion would be that lower BDNF expression is a risk factor in developing Alzheimer's Disease. Miranda et al. (2019) finds conflicting evidence on the topic, however it is agreed that BDNF suppression can mark the progression

of symptoms of Alzheimer's. Still, both animal studies and clinical studies strongly suggest that dysregulation (up- and down-regulation) of neurotrophic factors plays an important role in the causes of many psychiatric disorders. BDNF is arguably the most important neurotrophic factor - Miranda et al. (2019), so it is plausible and currently studied that suppressed BDNF levels directly leads to abnormal neuronal function i.e. psychiatric disorders.

One main focus to prevent the effects in Figure 2 and the above paragraph from taking place is to stabilise the HPA-axis in individuals with higher stress levels, or disorders which are associated with chronic stress.

Stabilising the dysregulated HPA-axis

Argentieri et al. (2017, p. 330) points out that "no comprehensive review exists that has examined the epigenetic regulation of all HPA axis genes within the entire glucocorticoid regulatory pathway", by examining possible ways to regulate HPA-axis genes it may be possible to interrupt the maladaptive cycle.

Perla et al. (2014) explore how mindfulness meditation influences the HPA's biochemical process, exploring changes in *epigenetic regulatory enzymes* (which are genes involved in epigenetic modification) and inflammatory genes alongside cortisol levels. The epigenetic regulatory enzymes / genes that were highlighted by the study was the family of *histone deacetylases,* these are genes which remove the acetyl groups from sections of DNA (which generally increase gene expression) to reduce gene expression.

The authors designed an experiment, where participants would either engage in intentional (non-mindfulness) activities such as computer games, reading etc. or a mindfulness intervention that involves guiding participants to "non-reactive present-moment awareness". This was repeated for 8 hour days in small groups with consistent meditators (meditating consistently for 3+ years) placed in the mindfulness intervention treatment, and participants who don't consistently meditate placed in the intentional group. This would increase any changes due to mindfulness, in order to be able to better detect any effects.

The notable effects associated with mindfulness compared to the control were that HDAC2, HDAC3 and HDAC9 decreased. It is supported by evidence that HDACs regulate inflammation responses, and the authors found a significant downregulation of an inflammatory regulator gene referred to as RIPK2 in the mindfulness group. This downregulation correlates significantly with the expression of HDACs 2, 3 and 9.

By performing a *Trier psychosocial stress test* (TSST), which is an interview based stress prompt also used and explained by Lee and Sawa (2014), Perla et al. (2019) measured cortisol levels of both groups. In both groups faster (healthier) cortisol recovery was associated with lower levels of RIPK2 and HDAC2 specifically.

Most importantly the authors establish that there is no significant difference between the groups and their mindfulness, rather that the levels of HDAC2 and RIPK2 seem to predict a more impervious HPA-axis. Since the HPA-axis is intertwined with many systems, including the inflammatory system it is likely that HDAC2 which downregulates RIPK2 may modulate inflammation such that the HPA-axis is more stable. This presents a possible treatment using an already common drug of HDACs, specifically HDAC2 to prevent HPA-axis dysregulation and by extension the many associated stress illnesses.

Reverting BDNF suppression

Current depression treatments, while their processes are not fully known, have been found to boost neurotrophin production including those associated with the expression of the BDNF genes. As mentioned beforehand, studies have found that abnormal levels of BDNF expression leads to behaviours implicated in depression and many other psychiatric diseases. Over-expression of BDNF functions (such as current depression treatments) results in learning and memory impairments alongside many unknowns which may also be unhealthy and likely undermine treatment (Cunha et al. 2019).

Roth et al. (2009) looks specifically at the effects of early life maltreatment (stress) on rats in addition to any influence to their offspring. They found maltreated pups had much more methylation of the BDNF DNA (approximately 2/3 more) which is also supported by the findings of Naert et al. (2011). These methylation changes were lifelong and somewhat *congenital* (present from birth) in the offspring of maltreated pups, most importantly these changes could not be reversed by cross-fostering or stress-free environments.

Rather than trying to over-express or boost the production neurotrophins (such as BDNF), targeting the suppressed BDNF sequence may avoid unnecessary side-effects and overtreatments seen by Cunha et al. (2019). Roth et al. (2009, pp. 765-769) tested the effects of *zebularine*, which is a drug that inhibits DNA methylating, and is thought to also actively demethylate DNA. When comparing against daily doses of saline, 7 days of zebularine doses was found to decrease many methylated sections of BDNF DNA. This re-normalised BDNF levels to much closer to the control, and thus healthy levels.

Conclusion

It’s established above the importance of treating the effects of adverse stress and the cascading effects HPA-axis dysregulation has on other physiological systems. The current major concern is the brain and the psychological diseases associated with BDNF suppression (Miranda et al. 2019). The shared use of the BDNF gene between systems leads to suppressed BDNF expression which retains long after stressors are removed (Roth et al. 2009).

The two treatments reviewed target either the first epigenetic link (HPA-axis maladaptation) or the final epigenetic link (BDNF suppression) between stress and psychological illness. The underlying gene expression measured shows a link between HDAC2 expression and a more resilient HPA-axis (Argentieri et al. 2017). This could be prompted through pharmacological use of HDAC2, however this treatment likely would leave more permanent effects that occur via methylation such as BDNF suppression unchanged (Chatzoffis et al. 2021). Roth et al. demonstrate it is feasible, rather than the current treatments of additional neurotrophins to make up for BDNF suppression, to return BDNF expression to normal levels without risk of unhealthily high neurotrophin levels.

These studies suggest that it is possible to both prevent and treat long-lasting effects of abnormal stress via epigenetic pathways without over-treatment or adverse side-effects.

z5421232

References

Argentieri, M. A., Nagarajan, S., Seddighzadeh, B., Baccarelli, A. A., & Shields, A. E., 2017, ‘Epigenetic Pathways in Human Disease: The Impact of DNA Methylation on Stress-Related Pathogenesis and Current Challenges in Biomarker Development’, *EBioMedicine*, vol. 18, pp. 327–350. DOI: 10.1016/j.ebiom.2017.03.044

Chatzittofis, A., Boström, A., Ciuculete, D. M., Öberg, K. G., Arver, S., Schiöth, H. B., & Jokinen, J. , 2021, ‘HPA axis dysregulation is associated with differential methylation of CpG-sites in related genes, *Scientific reports*, vol. *11, no.* 1, pp. 20134, DOI: 10.1038/s41598-021-99714-x

Cunha, C., Angelucci, A., D'Antoni, A., Dobrossy, M. D., Dunnett, S. B., Berardi, N., & Brambilla, R. , 2009, 'Brain-derived neurotrophic factor (BDNF) overexpression in the forebrain results in learning and memory impairments, *Neurobiology of Disease*, vol. 33, no. 3, pp. 358–368, DOI: 10.1016/j.nbd.2008.11.004

Lee, R. S., & Sawa, A., 2014, 'Environmental stressors and epigenetic control of the hypothalamic-pituitary-adrenal axis', *Neuroendocrinology*, vol. *100, no.* 4, pp. 278–287, DOI: 10.1159/000369585

Miranda, M., Morici, J. F., Zanoni, M. B., & Bekinschtein, P., 2019, 'Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain', *Frontiers in Cellular Neuroscience*, vol. 13, DOI: 10.3389/fncel.2019.00363

Moore, D. S., 2017, 'Behavioral epigenetics', *WIREs Systems Biology and Medicine*, vol. 9, no. 1, accessed 1 October 2022. <https://wires.onlinelibrary.wiley.com/doi/full/10.1002/wsbm.1333?saml_referrer>

Naert G, Ixart G, Maurice T, Tapia-Arancibia L, Givalois L., 2011, 'Brain-derived neurotrophic factor and hypothalamic-pituitary-adrenal axis adaptation processes in a depressive-like state induced by chronic restraint stress', *Mol Cell Neurosci*, vol. 46, no. 1, pp. 55-66., DOI: 10.1016/j.mcn.2010.08.006

Perla, K., María, J. A., Marta, C., Melissa A., R., Antoine, L., Richard, J., D., 2014, 'Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators', *Psychoneuroendocrinology*, vol. 40, pp. 96-107, DOI: 10.1016/j.psyneuen.2013.11.004

Roth, T. L., Lubin, F. D., Funk, A. J., & Sweatt, J. D., 2009, 'Lasting epigenetic influence of early-life adversity on the BDNF gene' *Biological psychiatry*, vol. *65, no.* 9, pp. 760–769, DOI: 10.1016/j.biopsych.2008.11.028