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The Neurotrophic Hypothesis of Depression: An Exemplary Exploration of the Treatment Potential of Erythropoietin

Review

A purely neurotransmitter-based explanation of major depression and antidepressant action, such as the monoamine hypothesis, falls short to explain the delayed clinical onset of most agents in reference to the immediate neurochemical effects. Recently, in attempts to understand the psychobiological underpinnings of depression, the focus shifted to an involvement of intracellular signaling cascades, gene expression and protein translation. This review discusses evidence for the neurotrophic hypothesis of depression, which emphasizes stress-induced disruption of brain-derived neurotrophic factors (BDNF), second messenger systems, gene expression and subsequent neural atrophy and network changes that manifest as depressive symptoms in the etiology of depression. Within the framework of the neurotrophic hypothesis, the treatment potential of the cytokine Erythropoietin (EPO) is discussed. Research does show some promising results for EPO as an antidepressant agent, however more research on its efficacy on its own as well as a potential add-on treatment to standard antidepressant treatments is required.

Keywords: Depression, Neurotrophic Hypothesis, BDNF, Erythropoietin, Antidepressant.

INTRODUCTION

Major depressive Disorder (MDD) is one of the most prevalent and impairing forms of mental illnesses. According to the World Health Organization (WHO), MD affects over 300 million people worldwide and is predicted to become the leading cause of disease burden by 2030 (WHO, 2017; WHO, 2008), underlining the urgency for a better understanding of its etiology and potential treatments. This is particularly important since the available pharmacological antidepressant treatments, most commonly selective serotonin or norepinephrine reuptake inhibitors (SSRIs and SNRIs, respectively) have significant limitations in their time lag for treatment response and lack of effectiveness, leading to high rates of relapses and treatment-resistant depression (Duman & Li, 2012). Strikingly, 50 years after introduction of the first-line antidepressant treatment – SSRIs – the field of psychiatry still has not managed (1) to fully understand the etiological mechanisms underlying MD or (2) to develop more effective treatment strategies. In fact, treatment-resistance, the failure to respond to antidepressant treatment of adequate dose and duration, is a major problem, underlining the importance for developing new or additional therapeutic agents (Fava, 2003).

Over time, the understanding of the etiology underlying depression moved away from the classic monoamine hypothesis that held a deficiency in the monoamine neurotransmitters solely responsible for the development of MD. This shift was primarily based on the realization that neurochemical and therapeutic effects of antidepressants had very different time scales, with potentiation of monoamines

occurring within hours after drug administration, while clinical improvement can take up to weeks to set in (Vetulani & Sulser, 1975). Subsequently, research sought to identify neurobiological mechanisms underlying this delay, such as neuroadaptive changes that might occur in the days and weeks after antidepressant treatment initiation and could account for this therapeutic delay (Harmer, Duman, & Cowen, 2017). By doing so, the focus shifted towards abnormalities in monoamine receptors and subsequent deficits in downstream molecular events, such as the gene expression of growth factors (Stahl, 2013). The deficiency in MD would not lie in the monoamine levels or their receptors directly, but more in the downstream signal transduction occurring upon postsynaptic receptor binding (Stahl, 2013).

Moving away from the monoamine hypothesis, neuroplasticity theories of depression, including the neurotrophic hypothesis, became increasingly popular, emphasizing the involvement of intracellular signaling cascades, gene expression and protein translation as core mechanisms of antidepressant drug action and hence the etiology of depression. One theory, the neurotrophic hypothesis of depression, focuses on the repression of the brain-derived neurotrophic factor (BDNF) gene and consequently decreased BDNF levels, in the etiology of MD (Stahl, 2013; Hayley & Litteljohn, 2013). BDNF is a growth factor essential for cell survival, neurogenesis, synaptogenesis and neuroplasticity, with deficient levels being associated with cell atrophy in hippocampal and prefrontal areas that have in turn been implicated in MD vulnerability (Hayley & Anisman, 2013). Therefore, direct exogenous administration of growth factors or treatments that increase endogenous BDNF, may constitute promising antidepressant treatment strategies, especially for currently treatment-

resistant cases (Hayley & Anisman, 2013). One such compound is the immune cytokine erythropoietin (EPO), endogenously produced by the kidneys and currently used in the treatment of anemia. Yet, recent evidence also suggests some antidepressant potential of EPO due to its neurotrophic effects.

This review aims to discuss the neurotrophic mechanisms underlying the etiology of MD (i.e. the neurotrophic hypothesis of depression), before investigating the potential of EPO as an innovative and alternative antidepressant treatment agent.

The neurotrophic hypothesis of depression

The neurotrophic hypothesis of depression states that MD results from decreased neurotrophic support from growth factors, such as BDNF, and associated neuronal, glial and synaptic atrophy (Duman & Li, 2012). Research emphasizes involvement of BDNF in mood disorders and identified the BDNF polymorphism val66met as a risk factor for MD, bipolar disorder and anxiety (Duman & Monteggia, 2006). Additionally, there is evidence for atrophy in the prefrontal cortex (PFC), hippocampus and other limbic structures in depression and other stress-related disorders, suggesting a potential disease pathway of inflammatory or stress-induced growth factor depletion and subsequent brain atrophy and depressive symptoms in MD (Duman & Li, 2012). Such a common disease pathway would also account for the high level of comorbidity of up to 50% between MD and other neurological inflammatory diseases, such as Multiple Sclerosis or Parkinson's Disease (Hayley & Littlejohn, 2013).It is however unclear what might cause these deficits in neuroplasticity. At a molecular level,

chronic stress – one of the key risk factors for depression – has been linked to increased levels of extracellular glutamate, which in turn contributes to the excitotoxic damage associated with depression (Popoli et al., 2012). Additionally, animal and human studies have shown that stress or depression indeed decreases the expression of BDNF, with stress/depression and antidepressant treatment exerting opposing effects on neurotrophic factors (Duman & Monteggia, 2006). Post-mortem studies on depressed patients who committed suicide revealed reduced BDNF levels in the hippocampus (Dwivedi et al., 2003), whereas Chen, Dowlatshai, MacQueen, Wang, and Young (2001) identified increased BDNF levels in the hippocampal areas (dentate gyrus) in patients receiving antidepressant medication at the time of death as compared to untreated subjects. Differences between antidepressant classes were however not taken into account in their analysis (Chen et al., 2001). There are also several reports of decreased serum BDNF levels in depressed patients that could be reversed by antidepressant treatment (discussed in Duman & Monteggia, 2006).

These results are in line with decreased functioning of the mitogen-activated protein kinase/extracellular kinase (MAPK/ERK) signaling pathway, the primary signaling cascade for BDNF, found in depression (Dwivedi et al., 2001). Dowlatshai et al. (1998) identified a decrease in the transcription factor CREB and its downstream neurotrophic factor BDNF in MD patients after death, that were restored in those treated with antidepressants. Similarly, an increase in the BDNF receptor tropomyosin-related kinase B (TrkB), also part of the MAPK/ERK signaling pathway, was found after antidepressant treatment (Bayer et al., 2000). Accordingly, evidence exists suggesting that MD might stem from a downregulation of a complex second messenger signaling

cascade, leading to decreased expression of BDNF and its receptors (e.g. TrkB) and subsequently decreased neuroplasticity, synaptogenesis and increased atrophy within the CNS.

Hayley and Littlejohn (2013) propose how these molecular and cellular abnormalities might translate to changes on network and systems levels ("faulty wiring") that are ultimately responsible for depressive symptoms on the behavioral level. They argue that MD is likely the result of deficient wiring of emotional and fear circuitry and that neuroplasticity is essential in antidepressant treatment as it enables the "rewiring" of such circuits. This is in line with evidence from Drevets, Price, and Furey (2008) who identified alterations in gray matter volume and neurophysiological activity in emotional brain networks around the medial PFC, including limbic areas in subjects with recurrent depressive episodes. The medial PFC is part of the default mode network (DMN), essential for self-referential thinking and likely the neural correlate of negative rumination seen in MD (Hayley & Littlejohn, 2013). Depressed patients fail to appropriately down-regulate DMN activity during tasks and consequently get stuck in their self-focused negative rumination (Sheline et al., 2009). It is argued that deficiencies in neuroplasticity, caused by low BDNF levels, contribute to faulty strengthening rather than correcting or "rewiring" of these circuits (Hayley & Littlejohn, 2012).

These findings indicate that chronic or excessive stress can lead to increased extracellular glutamate and disruption of BDNF signaling, causing synaptic and behavioral deficits, which, when paired with genetic factors, might increase the risk for MD (Harmer et al., 2017).

As evident across all studies presented, antidepressant treatments at least partly seem to work via upregulation of these signaling pathways and subsequent BDNF. Notably, chronic, but not acute, antidepressant treatment leads to an upregulation of BDNF and an increased BDNF expression in hippocampus and PFC. At the same time, the therapeutic effect requires long-term (at least four weeks) use of antidepressant medication, supporting the notion that BDNF upregulation and alterations in functional and structural plasticity are necessary for antidepressant effects to occur (Duman & Monteggia, 2006). Thereby the neurotrophic hypothesis does manage to account for the time lag in treatment response common to antidepressants, such as SSRIs to some extent.

As shown, research strongly suggests the conceptualization of MD as a multi-causal syndrome. It likely involves a complex molecular pathway of stress-induced pro-inflammatory growth factor depletion, subsequent CNS atrophy and network changes that manifest as depressive symptoms. Consequently, one potential treatment strategy would be to reverse that growth factor depletion by targeting BDNF more directly. Considering that our current antidepressant agents do not work for all patients, exploring new treatment options is an absolute necessity.

Erythropoietin (EPO) as an antidepressant agent?

One such compound targeting BDNF with potential antidepressant effects is the cytokine EPO. It easily crosses the blood-brain barrier (a prerequisite for an agent to act on the central nervous system [Miskowiak et al., 2010]). It has been shown to

possess neuroprotective and neurotrophic effects (Miskowiak et al., 2010), such as protection from stress-induced apoptosis in the hippocampus and increased neurogenesis (Hayley & Littlejohn, 2013); additionally, it has been found to induce antidepressant-like effects in animal models of depression on the forced swim and novelty-induced hypophagia tests (Grigenti et al., 2009).

Support for EPO's potential as an antidepressant treatment agent in humans comes from studies of Miskowiak and colleagues (2010; 2008; 2014). In two different studies, neuronal responses to emotional faces (fearful, happy) was assessed in 24 healthy and 19 acutely depressed (i.e. current acute depressive episode) patients three to seven days after EPO vs saline administration (Miskowiak et al. 2008, 2010). In healthy volunteers, EPO improved self-reported mood for all three days post-administration, and enhanced activation in the left amygdala and right precuneus to happy and fearful expressions (Miskowiak et al., 2008), underlining its effect on emotional processing. In patients, there was a reduced neural response to fearful faces in comparison to happy faces in limbic and tempo-occipitoparietal regions post EPO as compared to baseline. This was accompanied by a reduction in fear recognition, similar to effects seen with antidepressant treatment (Miskowiak et al., 2010). Accordingly, although EPO was shown to have different neural effects in patients and healthy volunteers, its mood-improving and antidepressant effects were evident in both groups.

In another randomized, placebo-controlled trial with 79 patients with major depression it was shown that EPO significantly decreased depressive symptoms and increased quality of life and memory recall and recognition in treatment-resistant MD

up to 14 weeks post treatment (Miskowiak et al., 2014). Hence, besides reduced negativity bias in emotional processing, EPO seems to be particularly beneficial in treatment of neurocognitive symptoms of mood disorders (Miskowiak et al., 2014; 2016). Neural correlates of these neurocognitive effects were decreased hippocampal volume loss and activity changes in encoding and recall-related networks (Miskowiak et al., 2016).

Hayley and Littlejohn (2013) propose that on a molecular basis EPO might modulate the MAPK signaling pathway, finally leading to activation of anti-apoptotic factors (e.g. BDNF), increased neuroplasticity and induction of antidepressant effects. There is some support from preclinical studies for EPO increasing BDNF production and gene expression (Ma et al., 2016). However, a clinical study by Vinberg et al. (2015) on the other hand reported a downregulation of plasma BDNF after EPO treatment in treatment resistant MD, questioning whether the neuroprotective and antidepressant effects of EPO really do occur via BDNF upregulation. On that account, Kamal et al. (2011) provide evidence for decreased excitatory neurotransmission as underlying the neuroprotective effects of EPO.

DISCUSSION

This review aimed to investigate the neurotrophic hypothesis of MD as well as the treatment implications for the cytokine EPO.

There is support for a neurotrophic involvement in MD, as many studies report neural atrophy, reduced BDNF levels or expression and neuroplasticity in MD, that are

reversed by antidepressant treatments. Research underlines the multicausality in the etiology of MD, involving a complex signaling cascade of stress-induced pro-inflammatory growth factor depletion, subsequent CNS atrophy and network changes. However, it is very clear that the picture is even more complex than that, as there seem to be regional differences in the effects of BDNF; whereas, in line with the neurotrophic hypothesis, neuroplasticity in hippocampal and PFC regions is usually linked to antidepressant effects, increased neuroplasticity in the amygdala has been associated with depressive relapse (Hayley & Littlejohn, 2013). Accordingly, it certainly seems that BDNF is involved in the etiology of MD, but the directionality of that relationship is not as straightforward. Hence, more research on the exact involvement of BDNF in MD in animals as well as humans is needed.

Nevertheless, targeting BDNF as antidepressant treatment seems promising and EPO does show some antidepressant and mood-improving potential in both patients and healthy volunteers. Although its effects on BDNF expression are still debated due to contradictory results, there is some support for its antidepressant effects in regulating emotional processing and improving neurocognitive functioning. However, before EPO could actually be implemented as an add-on treatment for MD, more research on its efficacy and precise working mechanisms are certainly needed, in order to shed light on its effects on BDNF and to investigate other potential therapeutic mechanisms (e.g. anti-inflammation, decreased excitation) that might underlie its antidepressant properties.

Lastly, research needs to investigate EPO's safety profile. Currently, solely approved as a treatment agent for anemia, EPO has been linked to higher rates of

venous thromboembolism and mortality in these patients (Bennett et al., 2008). Considering these serious safety issues, it is important to determine EPO's long-term effects on patients with other indications, such as MD.

Despite all these points of caution, the neurotrophic hypothesis and the investigation of neuroprotective compounds, such as EPO, creates hope. Now, decades after the introduction of antidepressants, MD remains to be one of the most prevalent and impairing mental illnesses. As the currently approved antidepressant medications do fall short due to their delayed treatment response and because they are not effective in all patients, it is time to turn to alternative agents, such as EPO, and to ascertain their treatment potential.

While this review certainly provided evidence for the neurotrophic hypothesis of depression and the involvement of BDNF and neuronal atrophy in its etiology and treatment, it should be noted that it is unlikely to be the whole story. Rather, we should consider neurotrophic factors and their evidence as one piece of the multifactorial origin of MD, that might play a larger or smaller role depending on the individual. Not only is the neurotrophic hypothesis multifactorial by itself, but additional, interacting and interlinked factors, such as environmental and biological stress, monoamine dysregulation, disruption of emotional brain circuits and psychological vulnerability factors (e.g. a neurotic personality or trauma), must not be forgotten.

REFERENCES

Barbany, G., & Persson, H. (1992). Regulation of Neurotrophin mRNA Expression in the Rat Brain by Glucocorticoids. *Eur J Neurosci, 4*(5), 396-403

Bayer, T. A., Schramm, M., Feldmann, N., Knable, M. B., & Falkai, P. (2000). Antidepressant drug exposure is associated with mRNA levels of tyrosine receptor kinase B in major depressive disorder. Prog Neuropsychopharmacol *Biol Psychiatry, 24*(6), 881-888.

Bennett, C. L., Silver, S. M., Djulbegovic, B., Samaras, A. T., Blau, C. A., Gleason, K. J., . . . Henke, M. (2008). Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA, 299*(8), 914-924. doi:10.1001/jama.299.8.914

Chen, B., Dowlatshahi, D., MacQueen, G. M., Wang, J. F., & Young, L. T. (2001). Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry, 50*(4), 260-265.

Dowlatshahi, D., MacQueen, G. M., Wang, J. F., & Young, L. T. (1998). Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. *Lancet, 352*(9142), 1754-1755. doi:10.1016/S0140-6736(05)79827-5

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct, 213*(1-2), 93-118. doi:10.1007/s00429-008-0189-x

Duman, R. S., & Li, N. (2012). A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. *Philos Trans R Soc Lond B Biol Sci, 367*(1601), 2475-2484. doi:10.1098/rstb.2011.0357

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biol Psychiatry, 59*(12), 1116-1127. doi:10.1016/j.biopsych.2006.02.013

Dwivedi, Y., Rao, J. S., Rizavi, H. S., Kotowski, J., Conley, R. R., Roberts, R. C., . . . Pandey, G. N. (2003). Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. *Arch Gen Psychiatry, 60*(3), 273-282.

Dwivedi, Y., Rizavi, H. S., Roberts, R. C., Conley, R. C., Tamminga, C. A., & Pandey, G. N. (2001). Reduced activation and expression of ERK1/2 MAP kinase in the post-mortembrain of depressed suicide subjects. *J Neurochem, 77*(3), 916-928.

Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*, *53*(8), 649-659. doi:10.1016/s0006-3223(03)00231-2

Girgenti, M. J., Hunsberger, J., Duman, C. H., Sathyanesan, M., Terwilliger, R., & Newton, S. S. (2009). Erythropoietin induction by electroconvulsive seizure, gene regulation, and antidepressant-like behavioral effects. *Biol Psychiatry, 66*(3), 267-274. doi:10.1016/j.biopsych.2008.12.005

Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *The Lancet Psychiatry*, *4*(5), 409-418. doi:10.1016/s2215-0366(17)30015-9

Hayley, S., & Anisman, H. (2013). Neurotrophic paths in the treatment of depression. *J Psychiatry Neurosci, 38*(5), 291-293. doi:10.1503/jpn.130146

Hayley, S., & Litteljohn, D. (2013). Neuroplasticity and the next wave of antidepressant strategies. Front *Cell Neurosci, 7*, 218. doi:10.3389/fncel.2013.00218

Kamal, A., Al Shaibani, T., & Ramakers, G. (2011). Erythropoietin decreases the excitatory neurotransmitter release probability and enhances synaptic plasticity in mice hippocampal slices. *Brain Res, 1410*, 33-37. doi:10.1016/j.brainres.2011.06.059

Ma, C., Cheng, F., Wang, X., Zhai, C., Yue, W., Lian, Y., & Wang, Q. (2016). Erythropoietin Pathway: A Potential Target for the Treatment of Depression. *Int J Mol Sci, 17*(5). doi:10.3390/ijms17050677

Miskowiak, K. W., Favaron, E., Hafizi, S., Inkster, B., Goodwin, G. M., Cowen, P. J., & Harmer, C. J. (2010). Erythropoietin modulates neural and cognitive processing of emotional information in biomarker models of antidepressant drug action in depressed patients. *Psychopharmacology (Berl), 210*(3), 419-428. doi:10.1007/s00213-010 1842-7

Miskowiak, K., Inkster, B., Selvaraj, S., Wise, R., Goodwin, G. M., & Harmer, C. J. (2008). Erythropoietin improves mood and modulates the cognitive and neural processing of emotion 3 days post administration. *Neuropsychopharmacology, 33*(3), 611-618. doi:10.1038/sj.npp.1301439

Miskowiak, K. W., Macoveanu, J., Vinberg, M., Assentoft, E., Randers, L., Harmer, C. J., . . . Kessing, L. V. (2016). Effects of erythropoietin on memory-relevant neurocircuitry activity and recall in mood disorders. *Acta Psychiatr Scand, 134*(3), 249-259. doi:10.1111/acps.12597

Miskowiak, K. W., Vinberg, M., Christensen, E. M., Bukh, J. D., Harmer, C. J., Ehrenreich, H., & Kessing, L. V. (2014). Recombinant human erythropoietin for treating treatment-resistant depression: a double-blind, randomized, placebo-controlled phase 2 trial. *Neuropsychopharmacology, 39*(6), 1399-1408. doi:10.1038/npp.2013.335

Popoli, M., Yan, Z., McEwen, B. S., & Sanacora, G. (2011). The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nature Reviews Neuroscience*, *13*(1), 22-37. doi:10.1038/nrn3138

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., . . . Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proc Natl Acad Sci U S A, 106*(6), 1942-1947. doi:10.1073/pnas.0812686106

Stahl, S. M. (2013). Essential psychopharmacology: Neuroscientific basis and practical application (4th ed). Cambridge, UK: Cambridge University Press.

Vetulani, J., & Sulser, F. (1975). Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. *Nature*, *257*(5526), 495-496. doi:10.1038/257495a0

Vinberg, M., Miskowiak, K., Hoejman, P., Pedersen, M., & Kessing, L. V. (2015). The effect of recombinant erythropoietin on plasma brain derived neurotrophic factor levels in patients with affective disorders: a randomised controlled study. *PLoS One, 10*(5), e0127629. doi:10.1371/journal.pone.0127629

WHO. (2017, February). Depression Fact Sheet. World Health Organization. Retrieved 04 July 2017 from www.who.int/mediacentre/factsheets/fs369/en/

WHO. (2008). The global burden of disease: 2004 update. Geneva, Switzerland: WHO Press, World Health Organization 2008. Retrieved 04 July 2017 from www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf