The possible links between neurogenesis, stress and depression

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

The hypothalamic-pituitary-adrenal axis is part of the neuroendocrine system and has been shown to be a critical regulator of the stress response. It can be considered to be the command centre and communication feedback system that senses stressors. There is a complex interaction between structures that release hormones culminating in the release of glucocorticoids- cortisol in humans. There is a negative feedback loop which prevents the system becoming overactive. The response is terminated through the same circuit that activated it.
Under normal physiological conditions the hypothalamic-pituitary-adrenal axis maintains low levels of cortisol. When there is exposure to chronic stress the negative feedback loop is impaired leading to hyperactivity of the HPA axis and high levels of cortisol. Chronic stress is harmful. Some individuals are more susceptible to the effects of stress than others- however it is unclear why this is so (Anacker et al. 2012, Ebner et al. 2017). Levone (Levone et al. 2015) states that resilience is “the ability to cope with environmental challenges ensuring survival”. Resilient individuals do not develop stress related illnesses. Southwick (Southwick et al. 2005) states that it may be possible to enhance stress resilience using drugs that stabilise the hypothalamic-pituitary-adrenal axis.

Some depressed patients show a hyperactivity of the hypothalamic-pituitary-adrenal axis resulting in an increase in cortisol (Pierscionek et al. 2014). Patients whose HPA axis remains abnormal after treatment for depression, are more likely to relapse than those patients whose HPA axis returns to normal (Thomson et al. 2008).

**Adult Hippocampal Neurogenesis (AHN)**

A neuron is an electrically excitable cell that receives, processes and transmits information through electrical and chemical signals. Neurons make our brains work. Neurogenesis refers to the growth and development of neurons. In most of the brain, no new neurons are added. However, the development of new neurons continues during adulthood in two regions of the brain. Adult
Hippocampal Neurogenesis (AHN) occurs in the subgranular zone of the dentate gyrus which is part of the hippocampus of the brain.

**Hippocampal volume**

Post mortem studies in humans have shown that the hippocampal volume is often reduced in depression. Impaired neurogenesis results in neuronal loss. Stockmeier (Stockmeier et al. 2004) suggests that reduced hippocampal volume in depressed patients is due to an increase in cell packing density.

![Brain diagram](image1.png)

The green structures are neurons

As many as 700 new neurons are added to the human hippocampus every day (Spalding et al. 2013). Alongside neurogenesis there is a substantial death of cells, resulting in the population of neurons remaining almost static. The slow rate of neurogenesis and the small number of new-born neurons (as many of these cells die after birth), raises a question whether such few neurons may at all be of relevance to the function of the human brain (Anacker 2014). Adult Hippocampal Neurogenesis has been implicated in the behavioural neurobiology of stress related disorders, especially anxiety and depression. The
causal relationship between AHN and the development of anxiety and depression remains controversial.

The loss of new neurons may alter the vulnerability to the effects of factors involved in the aetiology of depression. These neurons are involved in a vulnerability/resistance to depression rather than triggering a depressive episode, so new neurons may help to buffer the brain against stress (Snyder et al. 2011, Anacker et al. 2012). An impaired adult hippocampal neurogenesis confers vulnerability to depression (Bambico et al. 2013). It can be hypothesised that a robust AHN confers some resilience to depression.

**Stress**

Stress exerts a potent effect on neurogenesis (Gould et al. 1998). Stress increases cortisol blood levels. Unpredictable, non-controllable stress increases cortisol levels and reduces neurogenesis. Predictable controllable stress also increases glucocorticoids but increases neurogenesis. Cortisol has differential effects depending on which environmental stimulus precipitates its release. In some situations cortisol promotes neurogenesis, whilst in others it can reduce neurogenesis.

Chronic stress can cause a dysfunction of the hypothalamic-pituitary-adrenal axis feedback regulation. An increase in cortisol:

- Inhibits cell proliferation
- Reduces cell survival
- Reduces differentiation of new cells

**Regulation of neurogenesis (Duman et al. 2001)**

Down regulation of neurogenesis is caused by:

- Glucocorticoids- seen in stress and depression(Gould 1998)
- Inflammation
- Ageing

Upregulation of neurogenesis is seen in the presence of:

- Oestrogen
- Chronic antidepressant treatment
- Learning
• Environmental Enrichment
• Physical exercise
• Electroconvulsive therapy (ECT)

**Depression**

Depression is a state of low mood and aversion to activity that can affect a person’s thoughts, behaviour, feelings and sense of well-being. Acute neurochemical changes can precipitate a depressive episode. Slower structural changes allow the depression to persist and increase the vulnerability to subsequent episodes.

Most studies to investigate the role of neurogenesis in stress and depression have been done using animal models. For ethical reasons it is not possible to design studies using human subjects. Ablation of adult hippocampal neurogenesis in rodents may be sufficient to potentiate depression and anxiety behaviours following a stressor (Thomson et al. 2008, Miller et al. 2015). Contradictory studies suggest this is not the case (Sahay et al. 2007, Levone et al. 2015) - reducing neurogenesis using x rays or cytotoxic drugs, does not induce depressive like behaviours per se (Santarelli et al. 2003, Bessa et al. 2009, David et al. 2009). The loss of new neurons may alter the vulnerability to the effects of factors involved in the aetiology of depression (Tanti et al. 2013). These neurons are involved in the vulnerability/resilience to depression rather than actually triggering a depressive response.

Santarelli (Santarelli et al. 2003) used a rodent model of depression where the depressive behavioural features were relieved using an antidepressant. AHN was then inhibited using localised x-ray irradiation. It was demonstrated that the antidepressant no longer worked- suggesting that particular antidepressant required a neurogenic dependent mechanism. Some antidepressants may have both neurogenesis-dependent and independent effects on mood and behaviour (David et al. 2009).

Some antidepressants can promote cell proliferation and generation of new neurons in the hippocampus. Malberg (Malberg et al. 2000) showed that chronic but not acute treatment with antidepressants increases neurogenesis. Antidepressants take several weeks to work- this is similar to the timeframe that it takes new born cells to become integrated functional neurons. Some
Antidepressants do not stimulate neurogenesis suggesting that the reduction in adult hippocampal neurogenesis alone is unlikely to induce depression. Young adult-born neurons have been shown to inhibit the overall activity of the dentate gyrus of the hippocampus, by recruiting local interneurons and inhibiting the activity of the dense network of mature granule cells (Anacker et al. 2017).

There is now considered to be a “Neurogenic Theory of Depression”. This theory offers new perspectives into the aetiology of anxiety and depression. The hypothesis that a reduction in adult hippocampal neurogenesis leads to depression is controversial (Petrik et al. 2012). Other conditions that increase AHN eg exercise, could also provide antidepressant effects. Neurogenesis may be particularly relevant for achieving sustained spontaneous remission from depressive symptoms (Anacker 2014).

**New treatments**

Drugs have been developed that target different stages of the HPA axis that culminates in the production of cortisol. Drugs that inhibit the synthesis of cortisol showed a resolution of depressive symptoms (Thomson et al. 2008). However these drugs are toxic, have a wide range of unpleasant side effects and are poorly tolerated. Drugs that block the glucocorticoid receptor have been developed, but again have a limited safety profile. Drugs that target the hormones Corticotropin Releasing Hormone and Adrenocorticotropic Hormone to block their production have been developed and these have been shown to prevent the reduction of neurogenesis in rodents. Their efficacy in humans has yet to be reported (Thomson et al. 2008).

Drugs that target the hypothalamic-pituitary-adrenal axis are an important part of future research to develop safe and effective treatments that overcome the negative effects of dysregulation of the HPA axis. Further trials to find drugs that target the HPA axis is exciting in improving the treatment of affective disorders.

**Treatment Resistance**

Current drug treatment fails in 20-30% of patients. These patients are termed “treatment resistant”. They may however respond to electroconvulsive therapy (ECT). Electroconvulsive therapy (ECT) is a more potent stimulator of cell proliferation than antidepressant medication (Warner-Schmidt et al. 2006).
Another more recently developed treatment for resistant depression is Transcranial Magnetic Stimulation (TCMS). TCMS has an antidepressant effect in humans reversing the effects stress has on the hypothalamic-pituitary-adrenal axis. TCMS may or may not enhance adult hippocampal neurogenesis. The literature is contradictory. Some studies state it does not stimulate cell proliferation (Henn et al. 2004, Malberg 2004). Vaidya (Vaidya et al. 2007) states TCMS does not appear to enhance adult hippocampal neurogenesis. Ueyama (Ueyama et al. 2011) suggests that AHN may be required for the antidepressant effect of TCMS. Ultimately the mechanisms underlying TCMS are currently unknown as the literature is contradictory. If AHN is not involved—this questions the fact that neurogenic changes are necessary for the mood elevating effects of antidepressant treatment.

Summary

- The hypothalamic-pituitary-adrenal (HPA) axis is a critical regulator of the stress response. There is a negative feedback loop which prevents the system becoming overactive.
- Chronic stress impairs the negative feedback loop leading to elevated levels of cortisol. Chronic stress is harmful. Some individuals are more
susceptible to the effects of stress than others. Resilient individuals do not develop stress related illnesses.

- Some depressed patients show a hyperactivity of the HPA axis resulting in increases in cortisol. Patients whose HPA axis remains abnormal after treatment for depression, are more likely to relapse than those patients whose HPA axis returns to normal.
- Hippocampal volume is often reduced in depression. This may be due to an increase in cell packing density.
- Adult Hippocampal Neurogenesis (AHN) is the continual generation of new brain cells in a particular brain area. Alongside neurogenesis there is a substantial loss of cells, resulting in the population of neurons remaining almost static.
- AHN has been implicated in anxiety and depression. The causal relationship between AHN and the development of anxiety and depression remains controversial.
- The loss of new neurons may alter the vulnerability to the effects of factors involved in the aetiology of depression. These neurons are involved in a vulnerability/resilience to depression rather than triggering a depressive episode, so new neurons may help to buffer the brain against stress.
- Antidepressants take several weeks to work. This is similar to the time frame it takes new born cells to become integrated functional neurons.
- Antidepressants that target the HPA axis are an important part of future research.
- Antidepressants may have neurogenesis dependent and independent effects on mood and behaviour. Some antidepressants promote neurogenesis whilst others do not. This suggests that AHN alone is unlikely to induce depression.
- Electroconvulsive therapy is a more potent stimulator of cell proliferation than antidepressant medication.
- Transcranial magnetic stimulation may or may not enhance AHN. The literature is contradictory.

The above information has summarised the attempts in the literature to link adult hippocampal neurogenesis to anxiety, stress and depression. The literature is contradictory in places. The search for novel drug treatments is an
exciting field in psychopharmacology. As treatment resistance is a well-known phenomena- the possibility of new drugs and other non- pharmacological treatments that perhaps enhance neurogenesis, is an exciting opportunity for scientists and clinicians to increase the range of treatment options available to manage psychiatric disorders.

REFERENCES


