DOES NEUROGENESIS RELATE TO DEPRESSION AND DO ANTIDEPRESSANTS AFFECT NEUROGENESIS?"

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SUMMARY

Depression is characterized by atrophy in several brain structures, with the hippocampus seemingly particularly affected. A wide variety of cellular mechanisms have been proposed for these structural modifications, including the regression of dendritic branching. While neurogenesis alone appears inadequate to produce such marked changes, an altered rate is likely to affect hippocampal function. There is also strong evidence for neurotransmitter and glucocorticoid-mediated effects on neurogenesis, providing routes for the action of antidepressants. We aim to show how neurogenesis relates to the 'conventional monoaminergic theory of depression' and its modulation by antidepressants.

Key words: depression – neurogenesis – neurotransmitters – glucocorticoids - trophic factors

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Introduction

Depression is characterized by atrophy in several brain structures, with the hippocampus seemingly particularly affected. A wide variety of cellular mechanisms have been proposed for these structural modifications, including the regression of dendritic branching. While neurogenesis alone is inadequate to produce such marked changes, an altered rate is likely to affect hippocampal function. There is also strong evidence for neurotransmitter and glucocorticoid-mediated effects on neurogenesis, thus providing routes for actions of antidepressants. We aim to show how neurogenesis relates to the 'conventional 'monoaminergic theory of depression' and its modulation by antidepressants.

Brain atrophy observed in depressed patients may be largely dependent upon the balance between atrophic and trophic factors

A marked atrophy of the hippocampus has been observed in patients with major depressive disorder. Bremner et al. (2000) found that patients with depression had a 19% smaller left hippocampal volume than comparison subjects and two MRI meta-analysis studies (Videbech 2004, Campbell 2004) indicated both reduced right and left hippocampal volume.

Furthermore, the extent of atrophy exhibits a temporal relationship in both unipolar and bipolar depression patients. Sheline et al. (1996) found smaller hippocampi volume in subjects suffering from prolonged depression and Deicken et al. (2003) showed right hippocampal neuronal atrophy in patients with familial bipolar disorder patients which correlated with increasing duration of the illness.

However these structural changes are not restricted to the hippocampus. Almeida et al. (2003) found late onset depression to be associated with right frontal lobe atrophy and Sheline (Sheline 2000) reported modifications in the amygdala, caudate nucleus and putamen, which make up an interconnected neural circuit. This evidence is supported by PET analysis (Videbech 2002). It is somewhat unsurprising that atrophy of frontal lobes and hippocampi (Czéh 2007) may lead to such mood disorders, since these brain regions are crucial for managing several executive functions such as memory, emotion and attention.

Brain atrophy during major depression may arise due to a combination of factors. A reduction in volume of individual neurons or glial tissue and shifts in ventricle fluid balance have been proposed. Czéh & Lucassen (2007) also suggest that apoptosis is less likely than previously thought, as it cannot account for the reversible reduction in hippocampal volume in depression. Whilst slowed neurogenesis would be insufficient to produce the amount of observed hippocampal atrophy, it may have an important role in hippocampal dysfunction. Dendritic debranching, as documented widely in pre-clinical studies, may be more involved in volume reduction (Czéh 2007). Like neurogenesis, dendritic shrinkage may arise from a disruption of the balance between trophic and atrophic factors (see below) normally responsible for neuroplasticity.

Hypercortisolaemia and Neurotransmitters may disturb the balance between trophic and atrophic factors

Interestingly, conditions such as back pain and obesity have been linked to frontal lobe (Apkarian 2004) and hippocampal atrophy respectively (Gustafson 2004). The correlations between back pain and obesity with brain atrophy suggest the possibility of another causative variable that may be increased in depression, in particular cortisol. Indeed, in the clinic, depressed patients hypersecrete cortisol (Vreeburg 2009).

This idea that chronic stress is associated with depression, particularly when one has little control over the stressful state, is supported by studies of patients with Cushing's syndrome. These characteristically hypercortisolaemic patients show both depressive features and atrophic changes in the hippocampus (McEwen 2005). Decreased dendritic morphology in hippocampal neurons was also shown (Woolley 1990) in rodent models with excessive exposure to glucocorticoids.

Santarelli et al. (2003) showed stressed rats exhibited a decrease in hippocampal neurogenesis and that this effect was decreased upon administration of antidepressant fluoxetine (Prozac). Although selective disruption of this neurogenesis in the dentate gyrus by X-ray irradiation blocked the behavioral effects of chronic antidepressant treatment, Czéh & Lucassen (2007) argue this X-ray irradiation may inherently induce microaneurysms or inflammatory changes that indirectly affect cell proliferation and hippocampal function. Furthermore, a reduction in neurogenesis by means other than stress did not produce depression, suggesting a lesser importance of changes in neurogenesis alone.

Hippocampal dysfunction contributes to neuroendocrine dysregulation and may mediate a vicious cycle of hippocampal damage and depressive symptoms, as proposed by the "glucocorticoid cascade hypothesis" (Sapolsky 1986). The hippocampus is responsible for mediating the cortisol-induced feedback inhibition of the Hypothalamus-Pituitary-Adrenal (HPA) axis. Regression of dendritic processes, inhibition of neurogenesis and increased cell death in the hippocampus due to excessive exposure to glucocorticoids (Sapolsky 2000) may cause a reduction in this feedback inhibition of corticotrophin releasing factor (CRF) secretion.

Hypercortisolaemia in depression is manifest at several other levels in addition to the hypersecretion of CRF, including impaired glucocorticoid-receptor-mediated negative feedback and adrenal hypersensitivity to circulating adrenocorticotropic hormone (ACTH) (Krishnan 2008).

The mechanism by which cortisol causes brain atrophy may depend on an altered balance between trophic and atrophic intracellular factors in favour of the latter. Regulation of this balance is dependent on the mitochondria, and depressed patients exhibit mitochondrial abnormalities at the structural, molecular, and functional levels (Shao 2008). The energy metabolism deficits in patients with depression may be widespread, as suggested from data demonstrating reduced mitochondrial ATP production rate and increased mitochondrial DNA deletions in patients compared with control subjects (Gardner 2003).

Glucocortiocoid-mediated neurotoxicity may arise from excess activity of excitatory neurotransmitters such as glutamate. They increase glutamate concentrations in the hippocampal synapse (Moghaddam 1993), (Moghaddam 1994), (Lowy 1994), glutamate accumulation in response to excitotoxic insults in the hippo-

campus (Stein-Behrens 1992), (Stein-Behrens 1994), (Chou 1994) and free cytosolic calcium concentration in hippocampal neurons, enhancing cell death. Additionally, cortisol decreases the efficiency of the glucose transporter to further reduce cellular nutrient supply. Gene transfer techniques that increase glucose transport in the hippocampus buffer against neurotoxicity (Sapolsky 2000), illustrating the importance of this cortisol-mediated effect.

In addition to enhancing the effect of atrophic factors, glucocorticoids eliminate activity-dependent increases in brain-derived neurotrophic factor (BDNF), a trophic factor essential in neurogenesis (Campbell 2004). Duman (2005) suggests exercise and enriched environments increase neurotrophic support and neurogenesis, which could mimic antidepressants and counter the effects of stress.

Furthermore, glucocorticoids decrease levels of BDNF expression in the dentate gyrus and pyramidal cell layer of hippocampus in rodents (Smith 1995). This effect may also be partly due to stress-induced increases in serotonergic transmission (Smith 1995, Vaidya 1997).

The idea that stress is dependent upon and influences monoaminergic systems has given rise to the "monoaminergic hypothesis of depression", which argues that 'too little monoamines' are responsible for the depressive state. Cerebral areas affected by MDD have significant noradrenergic and serotonergic innervation (Manji 2001), which may highlight the importance of how we perceive stress.

The serotonin transporter (SERT) gene exists as two alleles, which differ in the length of their promoter region, and are thus aptly named long and short alleles. Individuals with the short SERT gene are less capable of inhibiting fear responses (Pezawas 2005), less able to take up serotonin from the synapse, and show greater sensitivity to stress (Caspi 2003). Lesch found that low serotonin levels in monkeys result in less social success and subjects with two short alleles seem to be more negative in the evaluation of their personal role in events (Canli 2007).

It is fascinating that monoamines may interact with trophic factors. The BDNF gene also exists as two versions, due to a single nucleotide polymorphism (Val66Met). Weinberger suggests having the Val/Val genotype "exaggerates" the short SERT gene anxiety effect, and thus may make one more susceptible to depression (Pezawas 2008).

Key Trophic and Atrophic factors play a role in depression

Brain derived neurotrophic factor (BDNF) is a neurotrophic factor that is associated with neuronal survival and growth and has been shown to promote neurogenesis. It has been implicated in almost all major CNS disorders such as epilepsy, neurodegenerative and neuropsychiatric disorders such as depression (Binder 2004, Lee 2010).

BDNF mediates its effect through binding to receptors such as tropomycin receptor kinase B (TrkB). Its expression is closely regulated by neuronal activity (Lee 2010). BDNF decreases the activity of Bad and stimulates the production of Bcl-2. Bcl-2 is another trophic factor which stabilizes the mitochondrial membrane to inhibit the action of Bad. BAG-1, identified by Manji (Manji 2001), inhibits the action of cortisol and increases the effects of Bcl-2. These trophic factors evidently complement one another's actions to enhance neurogenesis.

Low BDNF serum levels have been suggested to play a major role in MDD (Lee 2010, Shimizu 2003). Patients were evaluated using Hamilton Depression Rating Scale (HAM-D). The study showed a significant negative correlation between serum BDNF levels and HAM-D score.

The neurokinin-1 (NK1) receptor is associated with transmission of pain and stress signals. It has been shown to play a role in regulation of affective behaviour through pharmacological and genetic inactivation of the receptor (Mantyh 2002). Duric and McCarson showed on animal models that gene expression of both NK1 receptor and BDNF was decreased in chronic pain and chronic stress (Duric 2005). They concluded that alterations in gene expression for BDNF and NK1 receptor may be a response to neuronal injury.

Interestingly, not all individuals are equally vulnerable to developing depression following a stressful event (Blugeot 2011). Several traits that confer vulnerability including low BDNF levels associated with normal corticosterone serum levels have been identified in animal studies.

Antidepressants enhance neurogenesis

Evidence for the influence of monoaminergic systems in depression comes mainly from studies of properties of antidepressants. Tricyclic antidepressants (TCA) are both NET and SERT inhibitors and influence both noradrenergic and serotonergic transmission. The newer antidepressants can be either selective for serotonergic system: selective-serotonin reuptake inhibitors (SSRIs) or noradrenergic and serotonergic system: noradrenaline and serotonin reuptake inhibitors (SNRIs).

The SSRI sertraline increases human hippocampal neurogenesis via glucocorticoid receptor (GR) mediated mechanism. There was an increased neuronal differentiation following 3-10 day treatment with sertraline, which was abolished by GR antagonist RU489. The mechanism involves PKA signalling and GR phosphorylation, that then mediates activation of genes involved in neurogenesis (Anacker 2011).

TCA imipramine has also been shown to induce human astrocyte differentiation and to increase the number of hippocampal synapses and neurons in animal models (Cabras 2010, Han 2011). Höschl identified 4 major areas of action of antidepressants (Höschl 2005).

Firstly, administration of imipramine over 28 days lead to a decrease in timing of novelty suppressed feeding in animals in new environment, which indicates a reduction in stress-induced anxiety. Secondly, prolonged administration of imipramine resulted in increased BrdU – a DNA synthesis marker, which hence indicates an increase in DNA synthesis. Thirdly, removal of subgranular zone of dentate gyrus diminished the above mentioned effects, which indicates its importance. Another study showed that antidepressants stimulate hippocampal neurogenesis by inhibition of p21 expression in the subgranular zone of hippocampus (Pechnick 2011). Finally, knock-out mice for 5-HT1A receptor did not show the above mentioned effects either (Parks 1998). Also 5HT1A agonists, like buspirone - an atypical antidepressant, are shown to be efficacious in treatment of anxiety and depression (Cohn 1989) and have been suggested to have rapid antidepressant properties (Kennett 1987).

Chiou and colleagues has shown in vitro that treatment of hippocampal rat stem cells with MAOI moclobemide induced differentiation into neuronal cells that exhibited features of serotonergic neurons (Chiou 2006). The effect has also been shown in vivo in chronically stressed mice (Li 2004).

Both SSRIs, TCAs and MAOI have also been shown to increase BDNF levels in frontal cortex in animal models (Balu 2008).

Lithium has been shown to increase BDNF levels that then promote survival and differentiation through TrkB receptor in animal models (Hashimoto 2002). Similarly valproate counteracts the effects of stress induced hypercortisolemia by suppressing CRF and increases BDNF levels that lead to increased neurogenesis and promote neuronal survival (Qiu 2014).

There is clinical evidence which suggests that ketamine, a non-selective NMDA receptor antagonist has rapid antidepressant properties, which are seen within hours of administration (Murrough 2013). The effects of ketamine last for about a week and are seen long after the drug has been eliminated from the body, which suggests a signalling cascade that results long term potentiation and changes in receptor expression (Sleigh 2014). It has been shown that ketamine increases glutamate signalling and AMPA receptor expression, that in turn results in increased BDNF release and increased synaptogenesis via mTOR mediated changes in gene expression (Duman 2012).

Conclusion

In a healthy brain there is a fine balance between trophic and atrophic factors. That balance is disrupted in depression in favour of atrophic factors, which leads to atrophy of neurons and loss of dendrites. Antidepressants induce long term changes in gene expression that shifts the balance back in favour of trophic factors.

GLOSSARY

BAD: Bcl-2-associated death promoter is a pro-apoptotic protein associated with initiation of apoptosis. It forms heterodimers with anti-apoptotic proteins and prevents them from stopping apoptosis (Adachi 2002).

BAG-1: chaperone regulator that increases the anti-apoptotic effects of Bcl-2 (Takayama 1995).

Bcl-2: B-cell lymphoma 2 is an anti-apoptotic protein found in outer mitochondrial membrane. Normally it prevents apoptosis by binding pro-apoptotic proteins such as Bax and Bak (Cleary 1986). Uninhibited Bak and Bax form pores in the outer mitochondrial membrane that mediate release of cytochrome c and initiation of apoptosis (Maglott 2011). Binding of Bcl-2 prevents pore formation and hence apoptosis (Cleary 1986).

BDNF: Brain-derived neurotrophic factor is a neurotrophic factor present in CNS and PNS. It promotes neuronal survival, differentiation and formation of synapses (Binder 2004).

mTOR: mechanistic target of rapamycin is a serine/threonine protein kinase that is involved in regulation of cell growth, proliferation and survival (Hay 2004).

TrkB: tropomycin receptor kinase B is a high affinity receptor for neurotrophins such as BDNF that trasduces BDNF signalling across the cell membrane (Malenka 2009).

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