Antidepressants, brain-derived neurotrophic factor and neuroplasticity

Alexis Lewis

Algoma University

Abstract

Depression is a major cause of disability showing an 18% increase from 2005 to 2015, now affecting approximately 300 million people worldwide. Depression is thought to be due to a chemical imbalance where antidepressants increase monoaminergic neurotransmission. However, due to the delayed clinical onset of antidepressant drugs compared to the immediate monoaminergic effects, these views are considered too simplistic and have required further investigation. Stress triggers depression and has been found to decrease neuroplasticity in brain regions associated with depression including the hippocampus and prefrontal cortex (PFC), affecting functioning of structures involved in learning and memory, attention and concentration, and the regulation of mood. Brain-derived neurotrophic factor (BDNF) is critical to numerous forms of neuroplasticity and is reduced by chronic stress as well. The precise molecular mechanisms of antidepressants are unknown; however, evidence of animal models and post-mortem patients suggests BDNF contributing to neuroplasticity may be involved in both the pathophysiology and treatment of depression. Due to the heterogeneity and complexity of the disease the pathogenesis remains poorly understood; therefore, investigating treatment mechanisms will allow for rapid acting antidepressants to combat the delay of therapeutic effects associated with antidepressant drugs.

Depression is a highly debilitating disease and leading cause of disability worldwide affecting nearly 17% of the global population (Kessler et al., 2003; Lopez & Murray, 1998; Pincus & Pettit, 2001; Wittchen et al., 2011). Depression is linked to other mood disorders such as anxiety (Kessler et al. 1996; Hirschfeld, 2001), along with chronic comorbidities including substance use disorders (Boden & Fergusson, 2011; Grant, 1995), cardiovascular disease (Schulman & Shapiro, 2008; Swardfager et al., 2011), dementia (Byers & Yaffe, 2011), and type two diabetes (Knol et al., 2006) resulting in significant secondary costs to society of approximately $83 billion annually in the United States alone causing social and economic burden (Greenburg et al., 2003).

Depression is a devastating mental illness and is characterized by symptoms of personal suffering, profound mental agony, feelings of sadness, difficulty thinking and concentrating, reduced motivation or hopelessness, anhedonia, anergia, irritability, low self-esteem, disrupted sleep, appetite and cognition, tendency to suicide and overall affects one's thoughts, behaviour, and sense of well-being (Nestler et al., 2002). Depression is also associated with a decrease in employment, disruption of interpersonal relationships, a reduction in general health, psychosocial impairment and premature mortality (Erikkson et al., 1998; Reynolds & Patel, 2017). Although prevalent and often long-lasting; depression can be treatable through cognitive behavioural therapy (Gartlehner et al., 2017), electroconvulsive therapy (Dierckx et al., 2012), transcranial magnetic stimulation (Lefaucheur et al., 2014), physical activity (Schuch et al., 2018), and yoga (Cramer et al., 2013), and pharmaceutical agents such as antidepressants (Kozisek et al., 2008), however, there is incomplete knowledge of the pathogenic mechanism of depression and antidepressant mechanism.

The pathophysiology of depression has been explained by the lack of availability of monoamines such as serotonin, dopamine or norepinephrine and that antidepressant drugs work by increasing the extracellular availability of amines and neurotransmission at the synaptic level by inhibiting reuptake or the breakdown of monoamines (Heninger et al., 1996). A fundamental issue with this explanation is the immediate effects of drugs on monoamine availability occurring within minutes or hours whereas their therapeutic effects take several days to weeks suggesting the dysregulation of monoamines is not the only underlying factor in depression (Heninger et al., 1996; Hyman and Nestler, 1996). This has led researchers to study the neurobiological processes that occur after the initiation of antidepressant treatment to discover the underlying cause of the delay of action.

Through studying downstream molecular events, and cellular and structural mechanisms, antidepressants have been shown to increase neuroplasticity upon exerting therapeutic effects (Tardito et al., 2006). The exact pathophysiology of depression and possible dysfunction of neuroplasticity remains poorly understood, however it is likely that a fundamental relationship exists. Neuroplasticity refers to ability of the nervous system to incorporate, respond to and adapt to environmental stimuli at the neuronal level resulting in structural and functional changes in response to different experiences (Pittenger & Duman 2008). As a result, neuroplasticity is associated with remodeling of neurons essential to normal functioning and contributes to neurogenesis, synaptogenesis, apoptosis, dendritic length and branching, spine density (Tardito et al., 2006). Neurons are continuously forming and removing connections in response to received information as a way to integrate and transmit signals across complex networks, therefore, neurons must be plastic to process and synthesize information to produce behaviour, and disruption of neural plasticity may result in disease (Pittenger & Duman 2008).

Neuroplasticity can be displayed through modulation of connections via strengthening or weakening; neurons are responsible for the strengthening of synaptic connections, or in other words, long-term potential (LTP) which represents the occurrence of learning and memory, as well as synaptic weakening, or long-term depression (LTD) which represents weakening of memories or unlearning (Tardito et al., 2006). Neuroplasticity also involves changes in neuronal hardwiring mediated by neurotrophic factors (Pittenger & Duman 2008). Neurotrophic factors play a critical role in the formation and plasticity of neuronal networks. BDNF is the most abundant neurotrophin with the highest concentrations found in the hippocampus and cortex, and is involved in the growth, differentiation and survival of neurons and promotes dendritic outgrowth and spine formation resulting in a neuroplastic effect (Kozisek et al., 2008). BDNF is an important factor in the regulation of neurogenesis and synaptic plasticity and may play a vital role in the delayed response of antidepressants. Tropomyosin-related kinase B (TrkB) is a protein kinase receptor required for normal development and survival of neurons in the peripheral nervous system and is the receptor for BDNF (Kozisek et al., 2008). The potential cellular mechanism of action of antidepressant drugs including synaptogenesis or neurogenesis may require both BDNF and its receptor TrkB.

Neuroplasticity is strongly influenced in the brain's adaptation to stress and may underlie depression where dysfunctional histological changes in the hippocampus, prefrontal cortex and other parts of the brain due to stress may explain the clinical features of depression as a disorder of the hardwiring of the brain, and not a state of chemical imbalance (Eriksson et al., 1998; Sousa & Almeida, 2002). Chronic stress alters neuronal circuits in the brain including intracellular signalling and synapse number and function. Rodent studies have demonstrated synaptic loss in cortical and limbic areas which control emotion, mood and cognition in response

to stress, mainly the PFC and hippocampus which are associated with depression (McEwen et al., 2015; McEwen & Morrison, 2013). Additionally, stress decreases the formation of new neurons in the adult hippocampus (McEwen et al., 2015), and brain imaging studies show that depression is associated with reductions in the volume of the prefrontal cortex and hippocampus, suggesting atrophy and disruption of connectivity (MacQueen & Frodi, 2011).

Stress is a major cause of depression, is associated with abnormal hypothalamic-pituitary adrenal (HPA) axis function such as hypersecretion of cortisol, and has been shown to have immense effects on neuroplasticity (McEwen et al., 2015; Tardito et al., 2006). Due to glucocorticoid receptors on neurons throughout the hippocampus and other brain regions, mild stress can favour neuroplasticity through cortisol stimulation of hippocampal and prefrontal cortex neurons facilitating learning and memory, however chronic stress can have opposite effects and overstimulate neurons leaving areas of the brain vulnerable to the effects of stress and depression (Sousa & Almeida, 2002). Animal models have been used to study the neurobiology of stress, depression and antidepressant action in humans as changes in the regulation of endocrine systems, learning and memory, and histology of certain parts of the brain and behaviour show strong resemblances between stressed animals and depressed humans (Shirayama et al., 2002). Stress-induced changes in the hippocampus include loss of dendritic spines, decrease in number and length of dendrites, loss of synapses, loss of glia, impairment of neurogenesis, and apoptosis resulting in a reduction in hippocampal volume observed in post-mortem animal models of stress and depression as well as in magnetic resonance imaging (MRI) studies of depressed humans (D'sa & Duman, 2002; Pittenger & Duman, 2008). The elevation of circulating cortisol during chronic stress response exerts neurotoxic effects on hippocampal neurons through glucocorticoid receptor and its downstream effects can negatively affect

learning and memory (Sousa & Almeida, 2002). Losing dendrites and synapses decreases synaptic networks and connectivity decreasing effectiveness of neurons. Furthermore, apoptosis, decreasing neurogenesis, and losing glia which plays an important role in neurotransmission, magnifies the impairment.

The hippocampus has projections to the dorsolateral prefrontal cortex, the ventral tegmental area and the hypothalamus. Stress-induced changes in the hippocampus could therefore impair not only hippocampal functioning but also functioning in these downstream areas. The connection to the dorsolateral prefrontal cortex may explain behaviour observed in depression as it has important cognitive functions such as attention and concentration. Additionally, the ventral tegmental area projects to the nucleus accumbens, therefore, impairment of the reward system may be the result of symptoms such as anhedonia. The hypothalamic dysfunction downstream to the hippocampus may explain some of the neuroendocrine and autonomic nervous system disturbances that characterize depression (Pittenger and Duman, 2008).

Stress-induced changes in the PFC of animals include loss of dendritic spines, atrophy of the dendritic tree, loss of synapses, and decreased number and size of glia (Pittenger and Duman, 2008). Post-mortem studies in depressed humans have shown a decrease in neuronal size, glial size and number, and overall cortical thickness (D'sa & Duman, 2002). The PFC regulates cognitive functions such as attention, concentration, learning and memory, and higher mental functions such as motivation and judgment, all of which are impaired in depression, perhaps as a result of the prefrontal changes associated with stress and depression. Reduction in number of spine synapse connections and dendrite complexity in the PFC and hippocampus could

contribute to decreased volume in these regions accompanied by a loss of normal control of mood and emotion observed in depressed patients.

Antidepressant treatments have been shown to oppose or reverse the effects of synaptic plasticity caused by chronic stress (D'sa & Duman, 2002). Due to the impaired function of cortico-limbic regions involved in mood and emotion regulation, it has been suggested that alterations in neurotrophins such as BDNF underlie impaired neuroplasticity and antidepressants may exert their therapeutic effects by enhancing trophic signaling on neuronal and synaptic plasticity (Kozisek et al., 2008). Antidepressant drug treatment increases expression of proteins associated with synaptic plasticity (D'sa & Duman, 2002), and there is extensive evidence that demonstrates a requirement for BDNF in synaptic plasticity.

Antidepressants work by increasing BDNF which is required for long-term potentiation and is responsible for learning processes and memory formation, and for long-term memory storage (Kozisek et al., 2008). At a cellular level, BDNF has a demonstrated role in increasing presynaptic neurotransmitter release, mobilizing synaptic vesicles at existing synapses and increasing synapse formation (Kozisek et al., 2008). In humans, brain BDNF levels have been found to be reduced in post-mortem samples from depressed patients and increased in patients receiving antidepressant treatment at the time of death (Chen et al., 2001; Karege et al., 2005). In animals, the forced swim test and learned helplessness paradigms are stress induced behavioural models used to mimic mood disorders in humans such as depression. BDNF infusions in mice produce an antidepressant response and if BDNF or TrkB are impaired, then treatment is not effective (Shirayama et al., 2002). These studies provide support for the findings that reduced BDNF expression contributes to depression, and that antidepressant treatment increases or

reverses this deficit and that BDNF-induced neuroplasticity contributes to the actions of antidepressants.

BDNF and TrkB also activate intracellular mechanisms which in turn activate enzymes and proteins involved in neuroplasticity (Kozisek et al., 2008). Antidepressants rapidly increase TrkB activation and signaling followed by a long-lasting increase expression of BDNF in the hippocampus and prefrontal cortex (Chen et al., 2001). The induction of BDNF is dependent on chronic treatment for two to three weeks and observed in different antidepressant classes including selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), monoamine oxidase inhibitors (MAOI), and even electroconvulsive shock, however is not seen in other types of psychotropic drugs. The end result of these intracellular signaling pathways is a stimulation of neurogenesis in the hippocampus, and an increase in glial cells, dendritic growth and branching, inhibition of apoptosis, synaptogenesis and synaptic strengthening in the PFC and hippocampus. The time course of these neuroplasticity changes are on par with the time course of antidepressant action, inferring that the neurohistological effects caused by antidepressants are responsible for the alleviation of symptoms.

The mechanistic actions of antidepressants remain unknown. Prior monoamine theories are incomplete since the action of antidepressant drugs have been established as more complex due to their mood-elevating effects occurring weeks after administration, whereas enhanced monoamines occurs immediately indicating they are not solely responsible. Animal models and post-mortem studies demonstrate reduced levels of brain-derived neurotrophic factor in depressed patients and increased levels upon treatment suggesting BDNF is implicated in the etiology and treatment of depression. BDNF is involved in neurogenesis in the hippocampus, as well as synaptogenesis and synaptic strengthening in both the PFC and hippocampus

demonstrating its role in neuroplasticity. Neuroplasticity is decreased in the hippocampus and prefrontal cortex in depressed patients indicating its role as a potential contributor to the delay of therapeutic effects associated with antidepressants. Due to the personal, social and economic burden of depression, understanding its pathogenesis is important for the development of faster-acting antidepressants and may be discovered through further investigation of BDNF signaling, neuroplasticity, and the mechanism of action of antidepressant drugs through these cascades.

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