Do antidepressants affect neurogenesis and how does neurogenesis relate to depression?

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Abstract

Depression is associated with atrophy in several brain structures, with the hippocampus seemingly most affected. A wide variety of cellular mechanisms have been proposed for these structural changes. While impaired neurogenesis alone is inadequate to account for such marked changes, an altered rate of neurogenesis is likely to affect hippocampal function. There is also strong evidence for neurotransmitter and glucocorticoid-mediated effects on neurogenesis, providing routes for actions of antidepressants. As a consequence of this, neurogenesis provides an explanation for the 'conventional monoaminergic theory of depression' and also an explanation for the modulation of neurogenesis, and therefore depression, by antidepressant medication.

Keywords: depression, neurogenesis, neurotransmitters, glucocorticoids, trophic factors

Introduction

Depression is associated with atrophy in several brain structures, with the hippocampus seemingly most affected. While modulated neurogenesis alone is inadequate to account for 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; such effects might provide a rationale for the modes of 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. Marked atrophy of the hippocampus has been observed in patients with major depressive disorder. Bremner et al. (1) found that the left hippocampal volume was, on average, 19% smaller than for comparison subjects, and two MRI meta-analyses (2, 3) indicated reduced volume of both the right and left hippocampi. The extent of atrophy appears to have a temporal relationship in both unipolar and bipolar depression patients. Sheline et al. (4) found smaller mean hippocampal volumes in subjects with prolonged depression, and Deicken et al. (5) showed that right hippocampal neuronal atrophy in familial bipolar disorder patients correlated with increasing duration of the illness.

Structural changes are not restricted to the hippocampus. Almeida et al. (6) found late-onset depression to be associated with right frontal lobe atrophy, and Sheline (7) reported changes in the amygdala, caudate nucleus and putamen, which make up an interconnected neural circuit. This evidence is supported by PET analysis (8). It is not surprising that atrophy of the frontal lobes and hippocampi (9) may be associated with such mood disorders, as these brain regions are crucial for managing several executive functions, memory, emotion and attention.

Brain atrophy in major depression may arise from a combination of factors. A reduction in volume of individual neurons or glial tissue and shifts in ventricle fluid balance have been proposed. Czéh and Lucassen (9) have suggested that apoptosis is less likely to be a key mechanism than was 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 (9). 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. Conditions as diverse as back pain and obesity have been linked to atrophy of the frontal lobe (10) and hippocampal atrophy respectively (11). The correlations between back pain and obesity with brain atrophy suggest the possibility of another causative variable that may be increased in depression, namely cortisol. Clinically depressed patients hypersecrete cortisol (12). The idea that chronic stress is associated with depression, particularly when the individual has little control over the stressful state, is supported by studies of patients with Cushing syndrome. Such characteristically hypercortisolaemic patients show depressive features and atrophic changes in the hippocampus (13). Decreased dendritic morphology in hippocampal neurons has also been shown in rodent models with excessive exposure to glucocorticoids (14).

Santarelli et al. (15) showed that stressed rats exhibited a decrease in hippocampal neurogenesis and that this effect was less with administration of the antidepressant fluoxetine (Prozac). Although selective disruption of this neurogenesis in the dentate gyrus by X-ray irradiation blocked the behavioural effects of chronic antidepressant treatment, Czéh and Lucassen (9) have argued that this X-ray irradiation may inherently have induced microaneurysms or inflammatory changes that indirectly affected 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" (16). The hippocampus is responsible for mediating the cortisol-induced feedback inhibition of the hypothalamic-pituitary-adrenal (HPA) axis. Regression of dendritic processes, inhibition of neurogenesis and increased cell death in the hippocampus due to excessive exposure to glucocorticoids (17) may cause a reduction in this feedback inhibition on 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) (18).

The mechanism by which cortisol causes brain atrophy may depend on an altered balance between trophic and atrophic 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 (19). 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 (20).

Glucocorticoid-mediated neurotoxicity may arise from excess activity of excitatory neurotransmitters such as glutamate. The increased glutamate concentrations in the hippocampal synapse (21-23), glutamate accumulation in response to excitotoxic insults in the hippocampus (24-26) and free cytosolic calcium concentration in hippocampal neurons, enhance cell death. Additionally, cortisol decreases the efficiency of the glucose transporter, further reducing cellular nutrient supply. Gene transfer techniques that increase glucose transport in the hippocampus buffer against neurotoxicity (17), 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 (27). Duman (28) has suggested that exercise and enriched environments increase neurotrophic support and neurogenesis, which could mimic antidepressants and counter the effects of stress. Additionally, glucocorticoids decrease levels of BDNF expression in the dentate gyrus and pyramidal cell layer of the hippocampus in rodents (29). However, this effect may also be partly due to stress-induced increases in serotonergic transmission (29, 30).

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' is responsible for the depressive state. Cerebral areas affected by major depressive disorder (MDD) have significant noradr-

energic and serotonergic innervation (31). It is through these noradrenergic and serotonergic pathways that we perceive stress and the depressed state.

It has been suggested that low BDNF serum levels play a major role in MDD (37, 39). In these two studies, a negative correlation has been shown between serum BDNF levels and Hamilton Depression Rating Scale (HAM-D) score. 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 (32), less able to take up serotonin from the synapse, and show greater sensitivity to stress (33). 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 (34).

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 has suggested that having the Val/Val genotype "exaggerates" the short SERT gene anxiety effect, and thus may make one more susceptible to depression (35).

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; it has been shown to promote neurogenesis. BDNF has been implicated in almost all major CNS disorders such as epilepsy, neurodegenerative conditions and neuropsychiatric disorders, including depression (36, 37). The effect of BDNF is mediated through binding to receptors such as tropomyosin receptor kinase B (TrkB). Its expression is closely regulated by neuronal activity (37). BDNF decreases the activity of BAD (Bcl-2-associated death promoter) 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, another trophic factor identified by Manji (38), inhibits the action of cortisol and increases the effects of Bcl-2. These trophic factors evidently complement one another in their actions to enhance neurogenesis.

The neurokinin-1 (NK1) receptor is associated with transmission of pain and stress signals, and has been shown to play a role in regulation of affective behaviour through pharmacological and genetic inactivation of the receptor (40). Duric and McCarson have shown in animal models that gene expression of both the NK1 receptor and BDNF were decreased in chronic pain and chronic stress (41). They concluded that alterations in gene expression for BDNF and the NK1 receptor may be a response to neuronal injury.

Not all individuals are equally vulnerable to developing depression following a stressful event (42). Several traits that confer vulnerability, including low BDNF levels associated with normal corticosterone serum levels, have been identified in animal studies.

Antidepressants enhance neurogenesis

Tricyclic antidepressants (TCA) are both noradrenergic and serotonergic inhibitors and so influence both noradrenergic and serotonergic transmission. The newer antidepressants in common use may be selective for the serotonergic system: selective serotonin reuptake inhibitors (SSRIs), or noradrenergic and serotonergic system: noradrenaline and serotonin reuptake inhibitors (SNRIs). It is these classes of antidepressants, TCAs, SSRIs, and SNRIs, which have been studied with regard to neurogenesis.

The SSRI sertraline increases human hippocampal neurogenesis via the glucocorticoid receptor (GR) mediated mechanism. Anacker et al. demonstrated that there was an increased neuronal differentiation following 3-10 days of treatment with sertraline, which was abolished by the GR antagonist RU489. The mechanism involves PKA signalling and GR phosphorylation, that then mediates activation of genes involved in neurogenesis (43).

The TCA imipramine has also been shown to induce human astrocyte differentiation and to increase the number of hippocampal synapses and neurons in animal models (44, 45). Höschl has identified four major areas of action of antidepressants (46). First, administration of imipramine over 28 days led to a decrease in timing of novelty suppressed feeding in animals in a new environment, which indicated a reduction in stress-induced anxiety. Second, prolonged administration of imipramine resulted in increased BrdU, a

DNA synthesis marker, indicating an increase in DNA synthesis. Third, removal of the sub-granular zone of the dentate gyrus diminished the above-stated effects, which indicated its importance. Another study showed that antidepressants stimulate hippocampal neurogenesis by inhibition of p21 expression in the sub-granular zone of the hippocampus (47). p21 (cyclin-dependent kinase inhibitor 1) is a cyclin-dependent kinase inhibitor (CKI) that is capable of inhibiting all cyclin/CDK complexes, particularly CDK2. Finally, knock-out mice for the 5-HT_{1A} receptor did not show the above-stated effects (48). 5-HT_{1A} agonists, such as buspirone - an atypical antidepressant - have also been shown to be effective in the treatment of anxiety and depression (49), and it has been suggested that they have rapid antidepressant properties (50).

Chiou and colleagues have shown in vitro that treatment of hippocampal rat stem cells with the monoamine oxidase inhibitors (MAOI) moclobemide induced differentiation into neuronal cells that exhibit features of serotonergic neurons (51). This effect has also been shown in vivo in chronically stressed mice (52). SSRIs, TCAs and MAOIs have been shown to increase BDNF levels in the frontal cortex in animal models (53).

Lithium has been shown to increase BDNF levels which then promote survival and differentiation through TrkB receptors in animal models (54). Similarly, valproate counteracts the effects of stress induced hypercortisolaemia by suppressing CRF and increases BDNF levels which lead to increased neurogenesis and promote neuronal survival (55).

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 (56). 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 in long-term potentiation and changes in receptor expression (57). It has been shown that ketamine increases glutamate signalling and AMPA receptor expression, which in turn results in increased BDNF release and increased synaptogenesis via mTOR-mediated changes in gene expression (58).

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 shift the balance back in favour of trophic factors.

Glossary

BAD (Bcl-2-associated death promoter): a pro-apoptotic protein associated with initiation of apoptosis. It forms heterodimers with anti-apoptotic proteins and prevents them from stopping apoptosis (59).

BAG-1: a chaperone regulator that increases the anti-apoptotic effects of Bcl-2 (60).

Bcl-2 (B-cell lymphoma 2): an anti-apoptotic protein found in the outer mitochondrial membrane. Normally it prevents apoptosis by binding pro-apoptotic proteins such as Bax and Bak (61). Uninhibited, Bak and Bax form pores in the outer mitochondrial membrane that mediate release of cytochrome c and initiation of apoptosis. Binding of Bcl-2 prevents pore formation and hence apoptosis (61).

BDNF (brain-derived neurotrophic factor): a neurotrophic factor present in CNS and PNS. It promotes neuronal survival, differentiation and formation of synapses (36).

mTOR (mammalian target of rapamycin): a serine/threonine protein kinase that is involved in regulation of cell growth, proliferation and survival (62).

p21 (cyclin-dependent kinase inhibitor 1): a cyclin-dependent kinase inhibitor (CKI) which is capable of inhibiting all cyclin/CDK complexes, particularly CDK2.

TrkB (tropomyosin receptor kinase B): a high affinity receptor for neurotrophins such as BDNF that transduces BDNF signalling across the cell membrane (63).

References

1. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. American Journal of Psychiatry. 2000 Jan 1;157(1):115-8.

2. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. American Journal of Psychiatry. 2004 Nov 1;161(11):1957-66.

3. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. American Journal of Psychiatry. 2004 Apr 1;161(4):598-607.

4. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proceedings of the National Academy of Sciences. 1996 Apr 30;93(9):3908-13.

5. Deicken RF, Pegues MP, Anzalone S, Feiwell R, Soher B. Lower concentration of hippocampal N-acetylaspartate in familial bipolar I disorder. American Journal of Psychiatry. 2003 May 1;160(5):873-82.

6. Almeida OP, Burton EJ, Ferrier N, McKeith IG, O'Brien JT. Depression with late onset is associated with right frontal lobe atrophy. Psychological Medicine. 2003 May;33(4):675-81.

7. Sheline YI. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biological Psychiatry. 2000 Oct 15;48(8):791-800.

8. Videbech P, Ravnkilde B, Pedersen TH, Hartvig H, Egander A, Clemmensen K, Rasmussen NA, Andersen F, Gjedde A, Rosenberg R. The Danish PET/depression project: clinical symptoms and cerebral blood flow. A regions-of-interest analysis. Acta Psychiatrica Scandinavica. 2002 Jul;106(1):35-44.

9. Czéh B, Lucassen PJ. What causes the hippocampal volume decrease in depression? European Archives of Psychiatry and Clinical Neuroscience. 2007 Aug 1;257(5):250-60.

10. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. Journal of Neuroscience. 2004 Nov 17;24(46):10410-5.

11. Gustafson D, Lissner L, Bengtsson C, Björkelund C, Skoog I. A 24-year follow-up of body mass index and cerebral atrophy. Neurology. 2004 Nov 23;63(10):1876-81.

12. Vreeburg SA, Hoogendijk WJ, van Pelt J, DeRijk RH, Verhagen JC, van Dyck R, Smit JH, Zitman FG, Penninx BW. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Archives of General Psychiatry. 2009 Jun 1;66(6):617-26.

13. McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism. 2005 May 1;54(5):20-3.

14. Woolley CS, Gould E, McEwen BS. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. Brain Research. 1990 Oct 29;531(1-2):225-31.

15. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science. 2003 Aug 8;301(5634):805-9.

16. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocrine Reviews. 1986 Aug 1;7(3):284-301.

17. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biological Psychiatry. 2000 Oct 15;48(8):755-65.

18. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008 Oct 15;455(7215):894.

19. Shao L, Martin MV, Watson SJ, Schatzberg A, Akil H, Myers RM, Jones EG, Bunney WE, Vawter MP. Mitochondrial involvement in psychiatric disorders. Annals of Medicine. 2008 Jan 1;40(4):281-95.

20. Gardner A, Johansson A, Wibom R, Nennesmo I, von Döbeln U, Hagenfeldt L, Hällström T. Alterations of

mitochondrial function and correlations with personality traits in selected major depressive disorder patients. Journal of Affective Disorders. 2003 Sep 1;76(1-3):55-68.

21. Moghaddam B. Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. Journal of Neurochemistry. 1993 May;60(5):1650-7.

22. Moghaddam B, Bolinao ML, Stein-Behrens B, Sapolsky R. Glucocortcoids mediate the stress-induced extracellular accumulation of glutamate. Brain Research. 1994 Aug 29;655(1-2):251-4.

23. Lowy MT, Wittenberg L, Novotney S. Adrenalectomy attenuates kainic acid-induced spectrin proteolysis and heat shock protein 70 induction in hippocampus and cortex. Journal of Neurochemistry. 1994 Sep;63(3):886-94.

24. Stein-Behrens BA, Elliott EM, Miller CA, Schilling JW, Newcombe R, Sapolsky RM. Glucocorticoids exacerbate kainic acid–induced extracellular accumulation of excitatory amino acids in the rat hippocampus. Journal of Neurochemistry. 1992 May;58(5):1730-5.

25. Stein-Behrens BA, Lin WJ, Sapolsky RM. Physiological elevations of glucocorticoids potentiate glutamate accumulation in the hippocampus. Journal of Neurochemistry. 1994 Aug;63(2):596-602.

26. Chou YC, Lin WJ, Sapolsky RM. Glucocorticoids increase extracellular [3H] D-aspartate overflow in hippocampal cultures during cyanide-induced ischemia. Brain Research. 1994 Aug 15;654(1):8-14.

27. Campbell S, MacQueen G. The role of the hippocampus in the pathophysiology of major depression. Journal of Psychiatry & Neuroscience. 2004 Nov.

28. Duman RS. Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. Neurobiology of Aging. 2005 Dec 1;26(1):88-93.

29. Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. Journal of Neuroscience. 1995 Mar 1;15(3):1768-77.

30. Vaidya VA, Marek GJ, Aghajanian GK, Duman RS. 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. Journal of Neuroscience. 1997 Apr 15;17(8):2785-95.

31. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nature Medicine. 2001 May;7(5):541.

32. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nature Neuroscience. 2005 Jun;8(6):828.

33. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003 Jul 18;301(5631):386-9.

34. Canli T, Lesch KP. Long story short: the serotonin transporter in emotion regulation and social cognition. Nature Neuroscience. 2007 Sep;10(9):1103.

35. Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. Molecular Psychiatry. 2008 Jul;13(7):709.

36. Binder DK, Scharfman HE. Mini review: Brain-derived neurotrophic factor. Growth Factors. 2004 Jan 1;22(3):123-31.

37. Lee BH, Kim YK. The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. Psychiatry Investigation. 2010 Dec 1;7(4):231-5.

38. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nature Medicine. 2001 May;7(5):541.

39. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N,

Okada SI, Iyo M. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biological Psychiatry. 2003 Jul 1;54(1):70-5.

40. Mantyh PW. Neurobiology of substance P and the NK1 receptor. The Journal of Clinical Psychiatry. 2002;63:6-10.

41. Duric V, McCarson KE. Hippocampal neurokinin-1 receptor and brain-derived neurotrophic factor gene expression is decreased in rat models of pain and stress. Neuroscience. 2005 Jan 1;133(4):999-1006.

42. Blugeot A, Rivat C, Bouvier E, Molet J, Mouchard A, Zeau B, Bernard C, Benoliel JJ, Becker C. Vulnerability to depression: from brain neuroplasticity to identification of biomarkers. Journal of Neuroscience. 2011 Sep 7;31(36):12889-99.

43. Anacker C, Zunszain PA, Cattaneo A, Carvalho LA, Garabedian MJ, Thuret S, Price J, Pariante CM. Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. Molecular Psychiatry. 2011 Jul;16(7):738.

44. Cabras S, Saba F, Reali C, Scorciapino ML, Sirigu A, Talani G, Biggio G, Sogos V. Antidepressant imipramine induces human astrocytes to differentiate into cells with neuronal phenotype. International Journal of Neuropsychopharmacology. 2010 Jun 1;13(5):603-15.

45. Han X, Tong J, Zhang J, Farahvar A, Wang E, Yang J, Samadani U, Smith DH, Huang JH. Imipramine treatment improves cognitive outcome associated with enhanced hippocampal neurogenesis after traumatic brain injury in mice. Journal of Neurotrauma. 2011 Jun 1;28(6):995-1007.

46. Höschl C. Neurotrofní účinky antidepresiv. Farmakoterapie 2005;(3):223-228.

47. Pechnick RN, Zonis S, Wawrowsky K, Cosgayon R, Farrokhi C, Lacayo L, Chesnokova V. Antidepressants stimulate hippocampal neurogenesis by inhibiting p21 expression in the subgranular zone of the hipppocampus. PLOS One. 2011 Nov 4;6(11):e27290.

48. Parks CL, Robinson PS, Sibille E, Shenk T, Toth M. Increased anxiety of mice lacking the serotonin1A receptor. Proceedings of the National Academy of Sciences. 1998 Sep 1;95(18):10734-9.

49. Cohn JB, Rickels K, Steege JF. A pooled, double-blind comparison of the effects of buspirone, diazepam and placebo in women with chronic anxiety. Current Medical Research and Opinion. 1989 Jan 1;11(5):304-20.

50. Kennett GA, Dourish CT, Curzon G. Antidepressant-like action of 5-HT1A agonists and conventional antidepressants in an animal model of depression. European Journal of Pharmacology. 1987 Feb 24;134(3):265-74.

51. Chiou SH, Ku HH, Tsai TH, Lin HL, Chen LH, Chien CS, Ho LL, Lee CH, Chang YL. Moclobemide upregulated Bcl-2 expression and induced neural stem cell differentiation into serotoninergic neuron via extracellular-regulated kinase pathway. British Journal of Pharmacology. 2006 Jul;148(5):587-98.

52. Li YF, Zhang YZ, Liu YQ, Wang HL, Yuan L, Luo ZP. Moclobemide up-regulates proliferation of hippocampal progenitor cells in chronically stressed mice. Acta Pharmacologica Sinica. 2004 Nov 1;25:1408-12.

53. Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I. Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. Brain Research. 2008 May 23;1211:37-43.

54. Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang DM. Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. Neuropharmacology. 2002 Dec 1;43(7):1173-9.

55. Qiu HM, Yang JX, Liu D, Fei HZ, Hu XY, Zhou QX. Antidepressive effect of sodium valproate involving suppression of corticotropin-releasing factor expression and elevation of BDNF expression in rats exposed to chronic unpredicted stress. Neuroreport. 2014 Mar 5;25(4):205-10.

56. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. American Journal of Psychiatry. 2013 Oct;170(10):1134-42.

57. Sleigh J, Harvey M, Voss L, Denny B. Ketamine–More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care. 2014 Jun 1;4(2-3):76-81.

58. Duman RS, Li N, Liu RJ, Duric V, Aghajanian G. Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology. 2012 Jan 1;62(1):35-41.

59. Adachi M, Imai K. The proapoptotic BH3-only protein BAD transduces cell death signals independently of its interaction with Bcl-2. Cell Death and Differentiation. 2002 Nov;9(11):1240.

60. Takayama S, Sato T, Krajewski S, Kochel K, Irie S, Milian JA, Reed JC. Cloning and functional analysis of BAG-1: a novel Bcl-2-binding protein with anti-cell death activity. Cell. 1995 Jan 27;80(2):279-84.

61. Cleary ML, Smith SD, Sklar J. Cloning and structural analysis of cDNAs for bcl-2 and a hybrid bcl-2/immunoglobulin transcript resulting from the t (14; 18) translocation. Cell. 1986 Oct 10;47(1):19-28.

62. Hay N, Sonenberg N. Upstream and downstream of mTOR. Genes & Development. 2004 Aug 15;18(16):1926-45.

63. Malenka RC, Nestler EJ, Hyman SE. Chpter 8: Atypical neurotransmitters In Sydor A, Brown RY. Molecular Neuropharmacology: A Foundation for Clinical Neuroscience (2nd ed.) 2009. New York: McGraw-Hill Medical.