

Review

Neurobiological factors in depression: A Review

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The compelling and evolving nature of depressive disorders, one of a family of related conditions referred to as the “affective spectrum disorders” and one of the most prevalent psychiatric disorders, may be underscored by the numerous hypotheses enunciated in the last three decades concerning the nature of the disorder. Depressive disorders are a group of illnesses associated with significant neurobiological changes involving structural, functional and molecular alterations in several areas of the brain. Since no single cause of depression has been identified, understanding the neurobiologic substrates or biomarkers underlying the disease will help unravel the complexity of the disease as well as provide mechanistic explanation for the action of antidepressants and new insights on the latency of action of antidepressants, a latency of action which is at present undesirable considering the serious social and economic cost of the disease. These new insights, such as histone deacetylase (HDAC) inhibitors, isoform 2 of the potassium-chloride co-transporter (KCC₂) blockers, N-Methyl-D-aspartate (NMDA) modulators and anti-apoptotics, endogenous enkephalin and cocaine-amphetamine regulated transcript (CART) peptides, melanin concentrating hormone (MCH) receptor antagonists, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) potentiators and mitochondrial-targeted treatments like small-molecule inhibitors of glycogen synthase kinase (GSK)-3, may help provide drugs with a higher rate of responders than presently-available medications, since recent studies suggest that alteration in neuroplasticity and cellular resiliency may be more closely related to the pathogenesis and pathophysiology of depression as well as the mechanism of action related to affective treatments.

Keywords: Depression, genetics, neuroendocrine, neurotransmitters, stress.

INTRODUCTION

Depressive disorders are common psychiatric conditions, with life-time prevalence in most countries estimated to lie between 8 to 10% (Andrade et al., 2003). Its early life-occurrence, chronicity and risk factor/co-morbidity for/with other illnesses such as coronary vascular disease and asthma (Oriafio, 2010) increase the challenge it poses to investigators seeking to unravel the complexity of its knots and tangles (Evans and Charney, 2003 ; Maes et al., 2010). Andrade et al (2003) found major depressive episodes (MDEs) to be strongly co-morbid with, and temporarily secondary to, anxiety disorders in all countries studied. According to WHO (2001) and Moret (2003), depression also known as major depressive dis-

order (MDD) is the leading global cause of years of life lived with disability and the fourth leading cause of disability-adjusted life-years. Disability-adjusted life-years is defined as the reduction in an individual's productive life and takes into account premature mortality. So, depression contributes significantly to the global burden of diseases and disability and is expected to be the second leading contributor to Global Disease Burden by 2020. Its symptoms of low mood, lack of energy, anhedonia, social withdrawal, feelings of guilt and hopelessness including deficits in psychosocial functioning (Nestler et al., 2002) may eventually culminate in attempted or completed suicide (Mulholland and Cooper, 2000). In fact, 50%-80% of completed suicides are associated with mood disorders and about 15% of patients suffering from depressive disorder commit suicide (Kasper et al., 1996), an enormous social cost (Wong and Licino, 2004).

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The contributory factors to the aetiology of major depressive disorder, generally called depression, are multifactorial and this review aims to summarise the key findings from the clinical literature regarding neurobiological factors in depression and their roles in maximising treatment outcomes. The role of genetics, stress and inflammation, chronobiology, the state of the neuroendocrine and immune systems, neurotransmitter functioning and energy metabolism is discussed. The role of the endogenous anti-depressant peptides such as the enkephalins and of chloride transporters in its causation is not fully defined though a clearer picture seem to be emerging for a role for the inhibition of the omnipresent pro-apoptotic glycogen synthase kinase-3 (GSK-3), which is known to be down-regulated by the neurotrophins, brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) acting via the neuroprotective protein kinase B (Akt) (Johnson-Farley et al., 2006).

Genetics and Depression

Depression is a complex and multifactorial trait with important genetic and non-genetic contributory factors. The life-time prevalence of major depressive disorder is at least 10% with the risk in women twice that in men. Major depressive disorder (MDD) is common and moderately (70%) heritable (Lesch, 2004). Recurrence and early age at onset characterize cases with the greatest familial risk (Kendler et al., 1994). Major depressive disorder and the neuroticism personality trait have been found to share similar genetic susceptibilities. High premorbid neuroticism scores are a robust prediction of future onset of major depressive disorder (Kendler et al., 1994). Most genetic studies of MDD have considered a small set of functional polymorphisms relevant to monoaminergic neurotransmission, which include functional polymorphism in the loci encoding the serotonin transporter, serotonin 2A receptor, tyrosine hydroxylase and catechol-o-methyltransferase while sequence variation in the CREB1 gene have been observed in depressed women (Zubenko et al., 2003).

Recent genetic association analyses examining polymorphisms in mono-aminergic genes provide little evidence to implicate true deficits in serotonergic, noradrenergic or dopaminergic neurotransmission in the pathophysiology of depression (Peizhong, 2011; Sanacora, 2008; Krishnan and Nestler, 2010) leading investigators to speculate that the concepts of monoamines, energy metabolism and mitochondrial dysfunction, and inflammatory pathways may be inter-related in the disease; while underlining the dominant role of neuroplasticity.

Chronobiology and Depression

Diurnal variation of mood and sleep disturbances belong to the core of classical symptoms that have linked depression to the circadian system. Eighty percent of depressive states are associated with comorbid insomnia (Fava et al., 2004). Serotonin plays an important part in sleep regulation and prefrontal cortical serotonin has been linked to mood disorders. The monoaminergic nuclei, including the locus coeruleus, the serotonergic dorsal and median raphe nuclei and the histaminergic tuberomammillary neurons promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep-promoting neurons of the ventrolateral preoptic nucleus. During sleep, the ventrolateral preoptic nucleus inhibits the monoaminergic-mediated arousal regions through GABAergic and glycinergic projections.

Depressive patients sleep at the wrong biological clock-time, and excessive day-time sleepiness (EDS) can arise from depression (Chellapa et al., 2009). Total sleep deprivation (TSD) has antidepressant effects while bright light augments the actions of antidepressants (Ushijama et al., 2003). Agomelatine, a melatonin agonist which is able to reset the internal circadian clock (Lee et al., 2010) and 5HT_{2c} antagonists potentiate each other while the orexin (OX1 and OX2) receptor antagonists are being tested in treatment of insomnia implicating a relationship between disruption of the normal sleep/wake rhythm and obesity-metabolic syndrome (Gami and Somen, 2004). Melanin concentrating hormone signalling (MCHergic signaling) promote REM sleep and depression (Lagos et al., 2011) and its receptor antagonists are being tried as antidepressants and anorexigenic agents (Tortorolo et al., 2011).

Stress and Depression

In a prospective longitudinal study, it was found that individuals with one or two copies of the short allele of the 5-HT promoter polymorphism exhibited more depressive symptoms, diagnosable depression and suicidality in relation to stressful life events than individuals homozygous for the long allele (Caspi et al., 2003). Chronic stress downregulates cAMP-response element binding protein (CREB) phosphorylation and indirectly downregulates B-cell lymphoma-2 (Bcl-2) and brain-derived neurotrophic factor (BDNF), factors which are essential for cell survival. BDNF-extra-cellular signal-regulated kinase (ERK)1/2-CREB-Bcl-2 cascade dysregulation may be a key mechanism via which prolonged stress induces atrophy of select vulnerable neuronal subpopulations (Charney et al., 2004).

The hypothalamic-pituitary-adrenal axis and depression

Stress increases ACTH output from the pituitary gland consequent upon the up-regulated CRH from the hypothalamus. The hypercortisolaemia subsequently loses its feedback inhibition on the raised CRH which then remains permanently elevated (Holsboer, 2000; Holsboer et al., 1987).

This hypothalamic-pituitary-adrenal (HPA) axis dysregulation is related to the causality of depression (Muller et al., 2000). A major focus of the investigation of the relationship between stress and neurobiological changes seen in mental disorders has been the hypothalamic-pituitary-adrenal (HPA) axis, both as a marker of the stress response and as a mediator of additional downstream pathophysiologic changes including loss of neuronal plasticity and resilience (Sapolsky et al., 2000; 1999). According to Holsboer and Barden (1996), there is considerable evidence that HPA dysregulation is causally implicated in the onset of depression and that mechanisms of action of antidepressant drugs include actions on the HPA system (Holsboer and Barden, 1996). Therefore great interest is given on the development of antagonists for the CRH receptors type 1 and 2, two key players in the HPA-axis pathway (Gilligan et al., 2009). Other possible antidepressant drug targets within the HPA system are vasopressin and glucocorticoid receptors (Scott and Dinan, 1998). Already, vasopressin antagonists are in clinical trials (Griebel et al., 2003).

Antidepressants reverse corticosterone-mediated decrease in BDNF expression (Dwidvedi et al., 2006) and Magarinos et al. (1996; 1999) showed that antidepressants can reverse the dendritic atrophy caused by hypercortisolaemia.

Immunology and Depression

Psychoneuroimmunology is an area generating much interest recently with the realisation that the mechanism of action of antidepressants is far more complex than is assumed by the monoaminergic theory of depression (Castanon et al., 2000; Boselli et al., 2007). Substance P (Tamaoki et al., 1991) and cytokines (Chourbaji et al., 2006) are known to cause depression, an effect which can be reversed by antidepressants. The depressive features seen in diseases such as asthma, type 2 diabetes mellitus and coronary artery disease may be due to the over-expression of pro-inflammatory cytokines.

Upstream signalling systems implicated in the mechanism of action of antidepressants: These upstream systems regulate glycogen synthase kinase-3 (GSK-3), the inhibition of which is an important target for antidepressants (Jope, 2011)

The Serotonergic System

There is reduced cerebrospinal fluid level of 5-hydroxyindoleacetic (5-HIAA), a metabolite of serotonin, in patients with major depression (Gibbons and Davis, 1986; Brown and Linnoila, 1990). Synaptic concentration of serotonin is low in major depression (Racagni and Popoli, 2004; Cheetham et al., 1989) though Cheetham et al., (1989) noted that there is no difference in serotonin turnover between controls and depressed suicide victims. There is desensitisation of 5-HT_{1A} receptors leading to blunted neuroendocrine and temperature responses to 5-HT agonists with supersensitivity of the somatodendritic 5-HT₂ receptors inhibiting release of serotonin. There is reduced 5-HT_{1A} receptor binding in living brain and post-mortem brain tissue (Owen et al., 1986). Also, there is upregulation of β -receptor in major depression (Beer et al., 1987) with abnormal signal transduction following 5-HT binding to receptor. The serotonin transporter (SERT) acts to recycle back serotonin into the presynaptic nerve ending and it is a target of selective serotonin reuptake inhibitors and tricyclic anti depressants. Antidepressants act on this upstream system but clinical effects take days to weeks to manifest (Charney et al., 2004).

The noradrenergic system

In depression, there is reduced CSF and urinary 3-methoxy-4-hydroxy-phenylglycol (Brunello et al., 2002). There is elevated plasma noradrenaline but there is blunted neuroendocrine response to clonidine (Leonard, 2000). In depression, there is altered α ₂-adrenoceptor and β -adrenoceptor density and responsivity in peripheral circulating cells (Esteban et al., 1999). Brains depleted of noradrenaline show no significant response to serotonin (Rantamaki et al., 2004) and norepinephrine-deficient mice lack responses to antidepressants drugs, including selective serotonin reuptake inhibitors (Cryan et al., 2004). The norepinephrine transporter (NET) recycles norepinephrine back into the presynaptic nerve ending and agents that can block this transporter and increase synaptic norepinephrine show efficacy as antidepressants. Imipramine which was discovered in 1957 (Ban, 2001) is capable of blocking the norepinephrine transporter, so also are the selective serotonin norepinephrine reuptake inhibitors (SSNRI) like duloxetine.

The dopaminergic system

There is reduced CSF concentration of homovanillic (HVA) in patients with depression (Leonard, 2000) with blunted neuroendocrine and temperature responses to dopamine agonists. The dopamine transporter recycles dopamine back into the presynaptic nerve ending and agents that block the transporter have efficacy as antidepressants (Perona et al., 2008). Brains depleted of dopamine respond poorly to antidepressants (Rantamaki et al., 2008). Prominent anhedonia and amotivation accompany depression in patients with deficiency of dopamine.

The cholinergic system

Cholinergic excess (Renshaw et al., 1997) has been implicated as a mechanism for the causation of depressive disorder with increased muscarinic receptor density in the brain of depressive-suicide victims; and cholinomimetics have depressogenic effects (Janowsky and Overstreet, 2000). Though Vaillant in 1969 noted that discrete cholinergic mechanisms do not play an important role in endogenous depression, cholinergic overdrive has been demonstrated to produce behavioural (such as lack of energy), neuroendocrine (such as increased β -endorphins and growth hormone), and polysomnographic (such as increased REM sleep and shortening of REM sleep latency) features of melancholia (Dilsaver, 1986), and melancholics exhibit state-independent supersensitivity to cholinergic drive (such as administering the centrally-acting physostigmine to Flinders rat lines sensitive to diisofluorophosphate). Muscarinic receptor blockade could at some point disrupt acetylcholine-nitric oxide-cGMP-PKG signalling to reduce 5-HT uptake (Miller et al., 1994), and cause antidepressant effects (Liebenberg et al., 2010), and this may also explain the enhancement of the antidepressant effect of the serotonin agonist, 8-OH-DPAT, by atropine (Hadjjeri et al., 2004).

The glutamatergic system

Stress increases glutamatergic signalling and antidepressants decrease N-methyl-D-glutamate (NMDA) receptor subunit expression (Paul, 2000). NMDA antagonists have antidepressant action (Michael-Titus et al., 2000) and prevent hyperglutamatergic excitotoxicity. Glucocorticoid activation leads to increased NMDA receptor throughput and increased calcium currents that could predispose to neurotoxicity. In fact, a large body of evidence implicates glutamatergic neurotransmission in stress-induced hippocampal atrophy and death.

The GABAergic system

There is reduced CSF and plasma GABA in depression and the findings of Levinson et al (2010) suggest that GABA_B neurophysiological deficits are closely related to pathophysiology of major depressive disorder (MDD) but Klumpers et al., 2010 found that HPA axis hypertactivity is partly due to reduced GABA-ergic inhibition. Nevertheless, antagonists of GABA_B receptor have been shown to have antidepressant effects (Pilc and Nowak, 2005) while Slattery et al., (2005) showed that GABA_B receptor-mediated antidepressant behaviour is serotonin-dependent.

The serotonin hypothesis did not explain downstream signalling that underpins neuroplasticity

The assumed biochemical bedrock for the monoamine theory of depression has been the documented supersensitivity of catecholamine receptors in the presence of low levels of synaptic serotonin. Elegant as this theory seemed, it did not explain the latency of action of antidepressants due to the downstream neuroadaptive changes (Murphy, 1990; Charney, 1998; Charney et al., 2004) and the cooperativity of the various monoaminergic signalling systems (Thomas et al., 2004; Millan et al., 2001).

The hippocampus and depression

The hippocampus is a neural structure in the medial temporal lobe of the brain, whose plasticity stands it in a good stead for studies in depression. It has distinctive curved shape that has been likened to the sea horse monster of Greek mythology and the ram's horns of Amun in Egyptian mythology.

Afferents to the hippocampus come from the entorhinal cortex via the perforant pathway. They relay to the hippocampal dentate gyrus which in turn relay to the CA3 neurons via the mossy fibres. Via Schaffer collaterals, CA3 neurons relay to CA1 neurons which then relay back to the entorhinal cortex via the subiculum thus completing the trisynaptic loop. The other parts of the limbic system are the amygdala, claustrum, septal complex, supramammillary area, the hypothalamus, thalamus and brain stem ventral tegmental area which form connections with the hippocampus. The limbic system controls emotion formation and processing, memory and learning.

Stress reduces hippocampal plasticity, hippocampal volume and hippocampal neurotrophic factors such as BDNF and IGF-1 (Johnson-Farley et al., 2006) while antidepressants (ADs) and BDNF reverse the effects of

stress (Duman and Monteggia, 2006). Also, an over-expression of histone deacetylase₅ (HDAC₅) in the hippocampus prevents antidepressant effect (Lee et al., 2010).

Neuroplasticity and depression

The issue of neuroprotection and neurotrophins is recognised as an important new lead in the quest for a deeper understanding of mood disorders and the mechanism of action of antidepressants and mood stabilisers (Duman et al., 1997; Altar, 1999; Siuciak, 1997). There is now a greater appreciation of the convergence of mechanisms between stress, depression and neuroplasticity (Pittenger and Duman, 2008) and that this is likely to lead to the identification of novel targets for more efficacious treatment. Manifestation of neuroplasticity in the adult CNS include alteration of dendritic function, synaptic remodelling and long-term potentiation (LTP) axonal sprouting, neurite extension, synaptogenesis and neurogenesis. Below is the sequence of the hypotheses on the pathophysiology and pharmacology of depression that have been enunciated since the 1960s (Racagni and Popoli, 2008 ; Maes et al., 2010) which shows the hypothesis of inflammation-oxidative stress and nitrosative stress (IO and NS) to be the most recent and seems related to the hypothesis of neuroplasticity.

1. Monoaminergic hypothesis 1960s-1970s: Depression is caused by a decreased availability of monoaminergic neurotransmitters. Antidepressants boost monoamine levels.
2. Monoaminergic receptor hypothesis 1980s: Depression is caused by abnormalities in monoamine receptors. Chronic antidepressants alter sensitisation state of receptors.
3. Hypothesis of signalling adaptations 1990s: Chronic antidepressants induce adaptive changes in post-receptor signalling cascades, and in gene expression.
4. Hypothesis of neuroplasticity 2000s: Chronic antidepressants change neuroplasticity, cellular resilience and synaptic plasticity.
5. Hypothesis of inflammation-oxidative stress and nitrosative stress 2010: The inflammatory and neurodegenerative hypothesis of depression is underpinned by the evidence that there is increased oxidatively-generated DNA damage in depression and this perturbs cellular resilience and synaptic plasticity.

Depression, Neurodegeneration and Anti-oxidants

It has been shown that there are increased plasma peroxides and serum oxidized low-density lipoprotein antibodies in major depression, biomarkers that suggest that inflammatory-oxidative and nitrosative (IO and NS)

pathways are involved in the increased incidence of both coronary artery disease and neurodegeneration in depression (Maes et al., 2010). Antidepressants increase the ratio of kynurenic acid/3-hydroxykynurenine (Kocki et al., 2011) and agents with significant antioxidant status such as furosemide, nifedipine and ascorbic acid have been shown to exhibit antidepressant-like activity. There is decreased antioxidant enzymes and membrane polyunsaturated fatty acids in schizophrenia and bipolar mood disorder patients (Ranjekar et al., 2003) who also have higher thiobarbituric acid reactive substances and DNA damage. Previously, it was shown in 2009 by Maes et al. that there is increased 8-hydroxy-deoxyguanosine, a biomarker of oxidative damage to DNA, in major depression and myalgic/encephalomyelitis /chronic fatigue syndrome (ME/CFS). The inflammatory and neurodegenerative hypothesis of depression (Maes et al., 2009b) is underpinned by the evidence that there is increased oxidatively-generated DNA damage in patients with major depression and ME/CFS and oxidative damage to DNA is a risk factor for atherosclerosis and neurodegeneration. The increased levels of interleukin-6 in depression are directly related to symptoms of traumatic stress and somatoform dissociation (Bob et al., 2010). These inflammatory-oxidative and nitrosative pathways are induced by a number of trigger factors, for example, psychological stress, strenuous exercise, viral infections and an increased translocation of LPS from gram-negative bacteria as obtains in 'leaky gut' (Maes et al., 2009). In cultured neurons, inflammatory proteins cause an increase in reactive oxygen species, membrane fluidity and apoptosis by 24 hours (Christov et al., 2004).

Reactive oxygen species and calcium homeostasis

Mitochondrial calcium is modulated by reactive oxygen and nitrogen species and sustained Ca²⁺ increase generates reactive oxygen species (ROS) (Richter, 1992). The formation of ROS causes the disruption of Ca²⁺ homeostasis and cell death (Manzl et al., 2004). Reactive oxygen species and p38 mitogen-activated protein kinase activate Bax to induce mitochondrial cytochrome c release and apoptosis (Gomez-Lazaro et al., 2007). Anti-excitotoxics such as nifedipine and furosemide (Our unpublished observation) that attenuate sustained Ca²⁺ increases have recently been shown to be beneficial in some animal models of depression and epilepsy implicating excitotoxic injury as a partial factor in the causation of depression and epilepsy.

Calcium homeostasis and depression

There is elevated basal and thapsigargin-stimulated intracellular calcium in platelets and lymphocytes of bipo-

lar patients (Hough et al., 1999) and store-operated calcium channels may be the source of the high intracellular calcium.

Neurotrophins and cellular plasticity and resilience

The family of receptors known as tropomyosin-related tyrosine kinase receptors (Trks) mediate neurotrophic factor signalling. Nerve growth factor (NGF) binds to TrkA and brain-derived neurotrophic factor (BDNF) binds to TrkB (Saarelainen et al., 2003). Phosphatidylinositol-3-kinase (PI-3K) is then activated; also, there is activation of mitogen-activated protein (MAP) kinase. MAP kinase cascade activation can inhibit apoptosis by inducing the phosphorylation of Bad (a major pro-apoptotic protein) and increasing the expression of Bcl-2 (a major antiapoptotic protein). The increased Bcl-2 expression involves cyclic adenosine monophosphate response – element binding protein (CREB). Bcl-2 is neuroprotective and exerts neurotrophic effects. The presence of TrkB, the high-affinity receptor for BDNF, in hippocampal neural progenitor cells is required for the neurogenic and behavioural actions of antidepressant treatments (Banasr and Duman, 2009). Antidepressants have been found to rapidly autophosphorylate TrkB but this activation does not occur in the brains depleted of serotonin or norepinephrine (Rantamaki et al., 2007) showing the brain monoamines to be critical mediators of antidepressant-induced TrkB activation. Nevertheless, Rajagopal et al (2004) have shown that TrkB could also be activated independently of neurotrophins.

Chronic stress down-regulates CREB phosphorylation and indirectly down-regulates Bcl-2 and BDNF (Chen et al., 1997). ERK1/2-MAP kinase-Bcl-2 signaling cascade has critical role in cell survival in the CNS. BDNF-ERK1/2-CREB-Bcl-2 cascade dysregulation may be a key mechanism via which prolonged stress induces atrophy of select vulnerable neuronal subpopulations (Trentani et al., 2002). Decreased levels of CREB, BDNF and TrkB receptor have been described in suicide victims.

Antidepressant mechanisms and neurotrophic signalling cascades

Antidepressants increase CREB phosphorylation and CREB-mediated gene expression in mice limbic region (Conti et al., 2002; Thome et al., 2001]. They also increase neurogenesis (Peng et al., 2008) of dentate gyrus granular cells.

So, while mood disorders are clearly not classical neurodegenerative diseases, they are in fact associated with impairment of cellular plasticity and resilience; an association that tend to support what Emil Kraepelin said years ago that mental illnesses may be linked with neurodegeneration.

Enhanced KCC₂ in Depression

The neuron-specific cation-chloride co-transporter, KCC₂, is down-regulated by furosemide and BDNF and chronic application of furosemide up-regulates BDNF mRNA (Szekeres et al., 2010). BDNF is the neurotrophic protein that is deficient in depression and neuropathic pain and its upregulation is necessary for antidepressant activity. Enhanced expression of KCC₂ has been observed in depression (Matrisciano et al., 2010) and its underexpression has been linked to antidepressant-like increased activity in mice (Stil et al., 2011). The down-regulation of KCC₂ may also explain the antidepressant-like effect (Oriaifo and Omogbai, 2010) and enhancement of long-term potentiation by furosemide (Wang et al., 2006) and KCC₂ blockers may have a neurogenic role (Reynolds et al., 2008). Recently, anxiolytic effects of the loop diuretics, furosemide and bumetanide, were reported in animal experiments (Krystal et al., 2012). The presently-used antidepressants such as imipramine (a tertiary amine tricyclic antidepressant (TCA) and sertraline (a selective serotonin reuptake inhibitor (SSRI) have important actions on long-term potentiation (LTP), down-stream signaling and neuroplasticity to explain their long-term or chronic effects.

Endogenous peptides and depression

Recently it has been shown (Grondin et al., 2011) that furosemide's induction of salt appetite may activate endogenous enkephalin peptides (Baamonde et al., 1992) that might have antidepressant roles and cross-sensitise mice to amphetamine. Also, cocaine-amphetamine transcript peptides have been shown to exhibit antidepressant effects (Peizhong, 2011) opening up more avenues to explore endogenous peptides.

CONCLUSION

In conclusion, given the multifaceted and complex nature of depression which has made a definite aetiology difficult to grasp, any new insight that might help elucidate its aetiopathogenesis, which presently appears multifactorial, is worth the attention of investigators, as this is the bedrock of a rational drug design.

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