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Duality of Antidepressants and Neuroprotectants

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Abstract

The co-morbidity of neuropsychiatric disorders, particularly major depressive disorder (MDD) with neurodegenerative diseases, in particular Parkinson's disease (PD) is now well recognized. Indeed, it is suggested that depressive disorders, especially in late life, may be an indication of latent neurodegeneration. Thus, it is not unreasonable to expect that deterrents of MDD may also deter the onset and/or progression of the neurodegenerative diseases including PD. In this review, examples of neuroprotective efficacy of established as well as prospective antidepressants are provided. Conversely, mood-regulating effects of some neuroprotective drugs are also presented. Thus, in addition to currently used antidepressants, ketamine, nicotine, curcumin, and resveratrol are discussed for their dual efficacy. In addition, potential neurobiological substrates for their actions are presented. It is concluded that pharmacological developments of mood-regulating or neuroprotective drugs can have cross benefit in co-morbid conditions of neuropsychiatric and neurodegenerative disorders and that inflammatory and neurotrophic factors play important roles in both conditions.

Keywords

Major depressive disorder; Antidepressant; Neuroprotection; Neurodegenerative disorders; Neurotrophic factors; Inflammatory mediators

Introduction

Neuropsychiatric and neurodegenerative diseases are rather complex medical problems underscored by the limited and not fully effective interventions. It is now well recognized that more often than not, a number of factors, particularly genetic and environmental, act together to bring about the disorder (Roy et al. 2014; Lopizzo et al. 2015). In general, genes provide the susceptibility or vulnerability component and the environment, either internal or external, provides the knockout punch. However, if either one of the two players, genetics or environment, is severe enough it can precipitate the disease by itself. Nonetheless, these devastating diseases eventually arise because of abnormalities within the neurobiological substrates, e.g., the neurotransmitter systems, receptor functions, transduction signals, etc., that impair neuronal plasticity and function. More recently, the concept of alterations in circuit connections "connectopathy" has been introduced in both neuropsychiatric as well as

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neurodegenerative diseases (Martin 2012; Castrén 2013; Di Benedetto et al. 2013; Bredt et al. 2015). Thus, understanding the neurobiological underpinnings is critical in eventual treatment for either disease. Recent reports indicate a strong association between neuropsychiatric disorders (particularly, major depressive disorder = MDD) and neurological diseases (e.g., Parkinson's disease = PD). Moreover, some common mechanisms involving neurotrophic and inflammatory factors may be responsible for both conditions. Building on above, this review starts with a brief introduction of MDD, current medications as well as promising new compounds including ketamine, nicotine, curcumin, and resveratrol for this condition. In each case, evidence of possible neuroprotective effects by the antidepressants is provided. Indeed, the duality of the effects of these compounds is a main focus of this review. Moreover, mechanism(s) of action of the compounds, vis-à-vis their interaction with neurotrophic and the inflammatory mediators, to the extent available, is discussed. It is concluded that most antidepressants and neuroprotectants may share a common mechanism of promoting neurotrophic factors while suppressing pro-inflammatory mediators and that these effects contribute to the effectiveness of an antidepressant as a neuroprotectant and vice versa.

Depression

Clinical depression, characterized by a despondent feeling, loss of interest in pleasurable activities, guilt, worthlessness, and trouble concentrating, is a serious medical illness that adversely affects a person's level of activity. It is also associated with abnormalities in appetite and sleep. In severe cases, it can lead to suicidal ideation and actual suicide. Several types of depression are identified. Major depression is manifested by a combination of symptoms that interfere with the ability to work, sleep, eat, and enjoy once pleasurable activities. These disabling episodes of depression can occur once, twice, or several times in a lifetime. Dysthymia, a less severe type of depression, involves long-term chronic symptoms that do not disable but keep one from functioning at "full steam" or from feeling good. Manic-depressive or bipolar is not nearly as prevalent as other forms of depressive illnesses and involves cycles of depression and elation or mania.

It is estimated that 121 million people in the world live with some type of depression. In 2013, an estimated 15.7 million adults aged 18 or older in the U.S. had at least one major depressive episode in the past year. This represented 6.7 percent of all U.S. adults (NIMH 2015). Curiously, 80 % of the people who have depression are not being treated, although the number of individuals diagnosed with depression increases each year and there is a tremendous loss of productivity and increased medical expenses, estimated to be over 200 billion dollars annually (Greenberg et al. 2015). The most serious and devastating final outcome of severe depression is suicide, which amounts to approximately one million people worldwide every year (WFMH 2012).

Etiology of Depression

Although as noted above, genetics plays a very important role in manifestation of depression, various conditions, particularly stress, have been identified as a culprit in precipitation of this condition. Indeed, animal studies confirm that administration of chronic

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mild stress can result in depressive-like symptoms and that this model is commonly used to understand the neurobiological substrates of this disease and/or investigate novel therapies (Hill et al. 2012; Wiborg 2013; Lopizzo et al. 2015). As depicted in the diagram below (Fig. 1), genetic factors provide the biological vulnerability that can be directly affected by stress which can lead to connectopathy and/or neurochemical imbalance and hence manifestation of depressive-like behavior.

Role of Neurotrophins

Substantial evidence indicates that impairments in cellular plasticity underlie the pathophysiology of severe mood disorders (Manji and Duman 2001; Manji et al. 2003; Villanueva 2013; Duman 2014; Haase and Brown 2015). Neurotrophins, in particular, brain-derived neurotrophic factor (BDNF) and its receptor TrkB, the tyrosine kinase receptor for BDNF, are critically involved in regulation of synaptic plasticity and hence are strongly implicated in the pathophysiology of mood disorders (Manji and Duman 2001; Manji et al. 2003). Indeed, polymorphism in the BDNF gene has been associated with depression and some antidepressant therapies (Colle et al. 2015; Lisiecka et al. 2015). Moreover, reduced BDNF levels are observed in postmortem brain samples and in the blood of depressed patients. In addition, hippocampal volume reduction, reflective of a reduction in neurogenesis, has been detected in both animal models of depression (Zhao et al. 2008; Tizabi et al. 2010) as well as in human postmortem studies (Sheline et al. 2003; Czeh and Lucassen 2007). Interestingly, hippocampal volume reduction in the animal model of depression was also associated with a reduction in hippocampal BDNF (Hauser et al. 2011). These reductions, however, are reversible by successful antidepressant treatment (Sheline et al. 2003; Czeh and Lucassen 2007; Tizabi et al. 2010). Hence, antidepressants may, through enhanced BDNF signaling, improve the ability of critical brain circuits to optimally respond to environmental demands and help recover from depression (Castrén and Rantamäki 2008; Mendez-David et al. 2013; Duman 2014). It is noteworthy that chronic mild stress that is frequently used to induce depressive-like behavior in animal models is also associated with a reduction in neurogenesis (Sapolsky 2004; Toth et al. 2008).

Role of Inflammatory Mediators

In addition to neurotrophic factors, important roles for inflammatory mediators are evident in pathophysiology of a variety of neuropsychiatric disorders including MDD (Felger and Lotrich 2013; Postal and Appenzeller 2015; Toben and Baune 2015). This is supported by the results of numerous studies indicating elevated levels of the pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β in plasma of depressed patients (Gold and Irwin 2009; Felger and Lotrich 2013; Toben and Baune 2015). That pro-inflammatory cytokines are directly implicated in MDD has been recently reviewed (Hurley and Tizabi 2013; Anderson and Maes 2014; Müller 2014; Ogłodek et al. 2014) and hence will not be discussed in detail here. However, it is of relevance to note that the depression induced by chronic stress may also be due to an increase in the release of pro-inflammatory cytokines (Maes et al. 2009; Song and Wang 2011), which in turn can cause a reduction in neurogenesis (Song and Wang 2011; Felger and Lotrich 2013; Ogłodek et al. 2014;

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Stepanichev et al. 2014). Indeed, there is a reciprocal interaction between cytokines and neurotrophic factors (Spedding and Gressens 2008).

Thus, both neurotrophic factors and inflammatory mediators may play important roles in pathophysiology of depression and response to antidepressants. A summary of such interactions is depicted in Fig. 2.

Current Antidepressants

The current antidepressants follow the general hypothesis of "Biogenic Amine Depletion" which suggests that low levels of serotonin, norepinephrine, or dopamine in the brain are responsible for the symptom manifestation. Hence, drugs in these categories primarily target the uptake or degradation of biogenic amines to enhance the synaptic availability of the neurotransmitters (see Table 1).

Neuroprotection by Current Antidepressants and Involvement of Neurotrophins

A number of earlier reports indicated neurotrophic effects of antidepressants, reflected in elevated levels of brain-derived neurotrophic factor (BDNF), particularly in the hippocampus, suggesting possible neuroprotective effects as well (Nestler et al. 2002; Xu et al. 2003). These findings included all clinically relevant tri- and tetra-cyclic drugs, selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine uptake inhibitors (SSNRIs), and monoamine oxidase inhibitors (MAOIs). Indeed, Sheline and colleagues found that depression may be associated with hippocampal volume loss and that antidepressants may protect brain from damage due to depression (Sheline et al. 2003). Lately, the same group has reported on possible prophylactic use of citalopram, a SSRI in Alzheimer's disease (AD), as this drug appears to help prevent formation of amyloid plaques in transgenic mouse model as well as in humans (Sheline et al. 2014). The potential use of other antidepressants in AD has been recently reviewed (Kim et al. 2013). In addition, several studies indicate possible utility of fluoxetine in stroke patients. However, controversy over fluoxetine's exact mechanism of action in stroke remains. Although fluoxetine may increase neurogenesis (Corbett et al. 2015; Imoto et al. 2015; Sun et al. 2015), its beneficial effect in stroke may be due to reducing inhibitory interneuron expression in the premotor cortex (Ng et al. 2015). Nonetheless, taken together, it may be suggested that elevated levels of neurotrophins in general and BDNF in particular following antidepressants administration are at least partially responsible for the enhanced neurogenesis and hence beneficial effects in neurodegenerative diseases such as AD. As for beneficial effects of current antidepressants in stroke and their exact mechanism of action in that regard, further investigation is needed.

Neuroprotection by Current Antidepressants and Involvement of Inflammatory Mediators

Although possible interaction of currently used antidepressants and inflammatory mediators has not been adequately explored, it is of relevance to note that depression associated with

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low-level neuroinflammation may be at least partially due to alterations in serotonergic and noradrenergic neurotransmission (O'Sullivan et al. 2009; Müller 2014; Ménard et al. 2015). Moreover, it has been shown that norepinephrine (NE) can suppress neuroinflammation mediated by activation of microglia and astrocyte. Hence, NE uptake inhibitors' therapeutic efficacy in depression may also be related to NE-mediated anti-inflammatory effects (O'Sullivan et al. 2009). Other investigators have also provided evidence of interaction between currently used antidepressants and inflammatory modulators. Thus, Uher et al. (2014) report that high basal levels of C-reactive protein (CRP), a marker of systemic inflammation, predict positive response to escitalopram (a serotonin reuptake inhibitor), whereas low basal levels of CRP predict a positive response to nortriptyline (a norepinephrine reuptake inhibitor). Moreover, evidence of in vitro and in vivo regulation of serotonin transporter function by pro-inflammatory mediators has been recently reviewed (Haase and Brown 2015).

Limitations with Current Antidepressants

Although the introduction of antidepressants into the medical field decades ago could be held as a scientific triumph, the fact that there is a significant delay in onset of action (it may take several weeks for the antidepressant to become effective) and that they are not effective in all patients, in addition to having undesirable side effects (e.g., anxiety, restlessness, weight gain, decreased sex drive, insomnia/sleepiness, fatigue, nausea, diarrhea/constipation, headache, etc.), indicates an urgent need to develop novel drugs with better efficacy and less side effects. In this regard, recent efforts have identified some new drugs, which will be discussed in brief here. The emphasis, however, is to show that all these possible medications also possess some neuroprotective properties.

It is also important to note that depression need not always be associated with neurodegeneration. Rather, changes in synaptic plasticity associated with decreases in neurotrophic factors and increases in inflammatory mediators are likely contributing neurobiological substrates. Fortunately, these changes are reversible, as treatment with effective antidepressants can normalize such abnormalities. On the other hand, neurodegenerative diseases that are associated with neuronal losses and can also trigger mood disorders may only be afforded a symptomatic relief, as no drug is yet available to reverse neuronal loss. Nonetheless, it would be of significant interest and relevance to evaluate any drug developed to retard neurodegenerative processes for possible mood stabilizing effects as well.

Novel Antidepressants

Ketamine

Ketamine is emerging as a very promising potent and fast-acting antidepressant, which appears to be well tolerated across patient groups, with only transient mild-to-moderate adverse effects during infusion (Abdallah et al. 2015). It is a non-competitive NMDA receptor antagonist and a derivative of phencyclidine (PCP) that blocks the NMDA receptor (Harrison and Simmonds 1985). Clinical studies have shown significant reduction of depressive symptoms within 72 h of ketamine administration (Berman et al. 2000; Zarate et

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al. 2006; Iadarola et al. 2015), and that a single sub-anesthetic dose of ketamine has rapid and sustained antidepressant effects in treatment-resistant patients suffering from major depressive disorder (Maeng et al. 2008; Iadarola et al. 2015; Kavalali and Monteggia 2015). Interestingly, ketamine's antidepressant effect requires activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, as NBQX, an AMPA receptor antagonist, can block ketamine's effects (Maeng et al. 2008; Koike et al. 2011). Indeed, it has been shown that AMPA itself can exert an antidepressant effect in an animal model of depression (Akinfiresoye and Tizabi 2013). Moreover, clinical studies indicate that expression of AMPA receptors is altered in patients with depression (Freudenberg et al. 2015). Thus, future studies on AMPA receptor subtype involvement in depression may offer novel pharmacological interventions.

Role of Neurotrophins and Inflammatory Mediators in Ketamine's Antidepressant Action

In a recent article examining the efficacy of ketamine as well as vagal nerve stimulation (VNS) in treatment-resistant depression, the role of BDNF and its receptor in the beneficial effects of both ketamine and VNS were highlighted (Shah et al. 2014). In addition, using conditional knockout mice, it was deducted that BDNF is required for the antidepressant-like effect of ketamine (Autry et al. 2011). Ketamine activates neurotrophin signaling through TrkB receptor (Autry et al. 2011; Duman et al. 2012; Duman 2014). Further support of neurotrophin involvement in ketamine's effect was provided in a recent randomized clinical trial, where plasma BDNF levels were found to be significantly higher following antidepressant response to ketamine (Haile et al. 2014). Interestingly, in regard to involvement of AMPA receptors, it has been demonstrated that positive modulators of these receptors can also induce BDNF, and that some antidepressants such as tianeptine may act by restoring neuronal plasticity through this neurotrophic factor (Spedding and Gressens 2008).

As indicated above, inflammatory processes may be key contributors to depression (Hurley and Tizabi 2013; Anderson and Maes 2014; Müller 2014; Ogłodek et al. 2014). Antidepressant effects of ketamine may also be due to its suppression of pro-inflammatory cytokines such as TNF-α and IL-6 (Taniguchi et al. 2001, 2004) and promoting the activity of anti-inflammatory cytokines such as IL-10 (Simma et al. 2013). Ketamine may also suppress the expression of pro-inflammatory cytokines induced by lipopolysaccharide (LPS), an exotoxin derived from the outer membrane of Gram-negative bacteria (Helmer et al. 2003a, b; Chang et al. 2009; Yang et al. 2013a). Indeed, peripheral and central anti-inflammatory effects of ketamine are receiving substantial attention in relation to its therapeutic potential (De Kock et al. 2013; Hurley and Tizabi 2013).

Ketamine as a Neuroprotectant

Several investigations have demonstrated neuroprotective effects of ketamine both in vitro and in vivo. Indeed, a review of neuroprotective effects of ketamine against ischemic damage was published in 2010 (Hudetz and Pagel 2010). Recent reports provide further evidence of neuroprotective effects of ketamine in damage induced by oxygen glucose deprivation (Emnett et al. 2013) and against spinal ischemia (Kakinohana 2014). Interestingly, a combination of ketamine and atropine may offer neuroprotection against

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toxic (organophosphate)-induced status epilepticus in mice (Dhote et al. 2012). A more recent review summarizes antiepileptic as well as neuroprotective effects of ketamine (Dorandeu et al. 2013). Although the exact mechanism for neuroprotection by ketamine is not at hand, it could be speculated that its enhancement of the neurotrophic factors and reduction of inflammatory response may contribute to its neuroprotective effects. In this regard, it would be of considerable interest to determine the exact roles of signal transduction molecules, as it was demonstrated that ketamine's protection against medial cerebral artery occlusion was associated with inhibition of neuron-specific P-CREB (phosphorylated CAMP response element-binding protein) dephosphorylation (Shu et al. 2012). It is also critical to note that ketamine's neuroprotection is dependent on its low concentration as higher doses can result in toxicities of their own (Schifilliti et al. 2010).

Thus, ketamine is a promising antidepressant with neuroprotective properties that is at least partially mediated through activation of neurotrophic factors and suppression of pro-inflammatory mediators.

Nicotine

Nicotine as an Antidepressant

A number of preclinical (Semba et al. 1998; Djuric et al. 1999; Tizabi et al. 1999, 2000, 2009, 2010; Kalejaiye et al. 2013) as well as a limited number of clinical studies (Pomerleau and Pomerleau 1992; Salin-Pascual et al. 1995; McClernon et al. 2006; Cook et al. 2007) have verified an antidepressant effect of nicotine. Indeed, the high incidence of smoking among depressed patients has generated the "self medication" hypothesis, which posits that these individuals derive some relief of their symptoms via inhaled nicotine (Cook et al. 2007; Moreno-Coutino et al. 2007; Spring et al. 2008). This hypothesis is further supported by the findings that nicotine-withdrawal induces depression, which likely contributes to higher failure rate of smoking cessation among depressed individuals (Borrelli et al. 1996; Covey et al. 1997; Tsoh et al. 2000; Glassman et al. 2001; Edwards and Kendler 2011). Thus, sufficient evidence for applicability of nicotine or nicotinic compounds in neuropsychiatric disorders including posttraumatic stress disorder and MDD has been recently provided (Barreto et al. 2015; Picciotto et al. 2015; Rahman 2015).

Nicotine as a Neuroprotectant

In addition to its antidepressant qualities, a number of epidemiological and empirical studies also suggest neuroprotective effects for nicotine. This contention is supported by findings of an inverse relationship between Parkinson's disease and smoking, which has been consistently demonstrated in various countries (Dorn 1959; Nefzger et al. 1968; Baumann et al. 1980; Baron 1996; Ross and Petrovitch 2001; Thacker et al. 2007). Moreover, in vitro and in vivo studies have shown that nicotine may protect against nigrostriatal damage induced by various compounds. Thus, in Parkinson's disease cell models, nicotine protects against endogenous substances such as salsolinol and aminochrome that selectively damage dopaminergic cells (Copeland et al. 2005, 2007; Das and Tizabi 2009; Ramlochansingh et al. 2011; Munoz et al. 2012). Similarly in animal studies, including non-human primates, it has been shown that nicotine delays Parkinson's disease-like symptoms induced by MPTP (Quik

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et al. 2006, 2009, 2014). Moreover, nicotine may also reduce L-Dopa-induced dyskinesia (Quik et al. 2014). A mechanism of nicotine protection against Parkinson's disease may involve inhibition of astrocyte activation and inflammatory suppression (Liu et al. 2012). Nicotine's modulation of neuroinflammation is further supported by a number of studies (Piao et al. 2009; Shi et al. 2009; Cui and Li 2010) and is believed to be mediated through its interaction with α7 nicotinic receptors (Cui and Li 2010). It is of relevance to note that the anti-inflammatory effects of nicotine may also be applicable to a variety of conditions including ulcerative colitis, septic kidney injury, and obesity, all of which can be precipitated or exacerbated by inflammatory processes (Lakhan and Kirchgessner 2011; Chatterjee et al. 2012).

Apart from its anti-inflammatory properties, nicotine may also modulate synaptic plasticity via its interaction with the neurotrophic mediators, particularly BDNF, which may also be responsible for its antidepressant and neuroprotective effects (Belluardo et al. 2000; Posadas et al. 2013; Yakel 2013; Barreto et al. 2015). Thus, nicotine or nicotinic agonists may offer novel intervention in depressive and/or neurodegenerative diseases, particularly PD, via their interaction with neurotrophic and/or inflammatory mediators.

Curcumin

Curcumin as an Antidepressant

Curcumin, the active ingredient in turmeric (Curcuma longa), has been shown to function as an antioxidant (Sharma 1976; Ruby et al. 1995; Sandur et al. 2007a, b), anti-inflammatory (Aggarwal and Harikumar 2009; Jurenka 2009), neuroprotectant (Singla and Dhawan 2012; Qualls et al. 2014), and antidepressant. The antidepressant effects of curcumin were originally reported in stress-induced depression models (Xu et al. 2005a,b; Li et al. 2007; Kulkarni et al. 2008; Bhutani et al. 2009), but we observed a dose-dependent antidepressant-like effect of curcumin in WKY rats, a non-induced animal model of depression (Hurley et al. 2012a). More recently, the effects of curcumin on depressive-like behavior in mice after LPS administration (Wang et al. 2014) and in unpredictable, mild stress-induced depressive-like behavior in rats (Zhang et al. 2014) were also reported. Clinically, curcumin was shown to be an effective antidepressant (Lopresti et al. 2014) as well as capable of enhancing the efficacy of currently used antidepressants (Yu et al. 2015).

Curcumin may have antidepressant activities with diverse mechanisms of action involving primarily neurotransmitters, transcription pathways, neurogenesis, the hypothalamic–pituitary–adrenal axis, and inflammatory and immune pathways, as demonstrated in various animal and human studies (reviewed in Tizabi et al. 2014; Seo et al. 2015). Hence, curcumin increases biogenic amines (e.g., dopamine, serotonin, and NE) in the cortex and hippocampus (Xu et al. 2005a, b; Kulkarni et al. 2008; Arora et al. 2011), up-regulates hippocampal BDNF (Hurley et al. 2012a; Liu et al. 2014a), reduces mRNA and protein of pro-inflammatory cytokines (e.g., TNF-α and IL-1β) as well as proteins involved in apoptotic pathways (e.g., *NF*-κ*B* and caspase-3) (Abe et al. 1999; Arora et al. 2011). Thus, multiple mechanisms including interactions with the neurotrophic and inflammatory mediators may be contributing to the antidepressant-like effects of curcumin.

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Curcumin as a Neuroprotectant

In regard to neuroprotection, it has been observed that societies that widely use curcumin show reduced incidence of inflammation-influenced and cognitive deficits (Chandra et al. 2001; Vas et al. 2001; Ng et al. 2006; Aggarwal et al. 2007). Indeed, anti-inflammatory effects of curcumin vis-à-vis suppression of IL-1β, tumor necrosis factor TNF-α, (Gupta et al. 2014; Yuan et al. 2015), and the nuclear factor NF-κB, considered a prototypical pro-inflammatory signaling pathway (Yang et al. Yang et al. 2014b; Yuan et al. 2015), as well as intracellular components of glial fibrillary acidic protein (GFAP), considered a marker of gliosis (Yuan et al. 2015), have been reported. Thus, curcumin may exert a neuroprotective effect against the 6-OHDA-induced rat model of PD (Yang et al. 2014aa) and may also protect axons from degeneration in the setting of local neuroinflammation (Tegenge et al. 2014). In addition, curcumin may ameliorate the adverse effects of the neurotoxin *N*-methyl *N*-nitrosourea in the cerebrum and cerebellum of mice (Singla and Dhawan 2012) and may exert a neuroprotective effect against ischemic spinal cord injury by decreasing inducible nitric oxide synthase as well as *N*-methyl-D-aspartate receptor expression (Zhang et al. 2013). Recently, it was demonstrated that curcumin as an anti-inflammatory and anti-oxidative agent can help myelin to repair, which can be of significant clinical relevance to multiple sclerosis (Mohajeri et al. 2015). These anti-inflammatory effects of curcumin together with its neurotrophic promoting effects (see above and Nam et al. 2014), make this compound of significant interest in both neuropsychiatric, particularly MDD, and neurodegenerative diseases, such as PD and AD (Darvesh et al. 2012; Tizabi et al. 2014).

However, two important points have to be considered in relation to therapeutic use of curcumin. The first point concerns its bioavailability as dietary curcumin exhibits poor bioavailability (Hamaguchi et al. 2010). This might be due to several factors including its insolubility in water, poor absorption, and rapid metabolism that need to be overcome for a more meaningful therapeutic intervention. In this regard, it has been suggested that addition of piperine could enhance curcumin's absorption (Hamaguchi et al. 2010). Interestingly, a clinical study where curcumin was combined with piperine showed significant efficacy in treatment of MDD (Panahi et al. 2015). The bioavailability of curcumin may also be increased by its dissolution in oil or cooking (Yang et al. 2013b). However, structural modification and development of novel curcumin derivatives that may be administered orally or intra-nasally may offer a more realistic approach.

The other important point concerns possible combination of curcumin or its more stable derivatives with current or other medications to treat depression and/or PD. This approach may be particularly beneficial since different drugs may act at different sites and offer a better control of inflammation, neurogenesis, and other processes (e.g., oxidation) that may contribute to the pathology of these diseases. In this regard, it is of interest to note that clinically, it was demonstrated that curcumin enhances the efficacy of current antidepressants (Yu et al. 2015). In addition, as discussed in this review, a number of novel compounds including ketamine, nicotine, and resveratrol (see below) that have shown potential usefulness in major depression and PD may be combined together for a potential additive or synergistic effect (Seidl and Potashkin 2011; Mythri and Bharath 2012; Brondino et al. 2014).

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Resveratrol

Resveratrol as an Antidepressant and Neuroprotectant

Resveratrol, a natural non-flavonoid polyphenol antioxidant, (3, 4', 5-trihydroxy-trans-stilbene), is a substance extracted from red grapes in the processing of wine, but it is also found in other fruit skins. Preclinical studies have shown the antidepressant-like effect of resveratrol in various rodent models including the corticosterone-induced depression in mice (Ali et al. 2015) and the Wistar-Kyoto rat model of depression (Hurley et al. 2014). Moreover, in both cases, the antidepressant effect of resveratrol was associated with an increase in hippocampal BDNF (Hurley et al. 2014; Ali et al. 2015). Interestingly, resveratrol also prevented depression and the impaired cognition induced by chronic unpredictable mild stress in rats, and resulted in an increase in hippocampal BDNF (Ge et al. 2013; Liu et al. 2014b).

In addition to its effect on neurotrophic factors, resveratrol also possesses anti-inflammatory effects as it significantly inhibits LPS-induced microglial activation and production of TNF-α, IL-1β, and nitric oxide (another proinflammatory factor) (Zhang et al. 2012; Pallàs et al. 2013). These properties of resveratrol are likely responsible for its various beneficial effects in neurodegenerative diseases and improvement of cognitive functioning. Indeed, a number of reports have highlighted possible application of resveratrol in ischemic and traumatic CNS injury (Sinha et al. 2002; Wang et al. 2002; Lopez et al. 2015), in AD (Vingtdeux et al. 2008; Rege et al. 2014), in PD (Tredici et al. 1999; Chen et al. 2007; Lofrumento et al. 2014; Fu et al. 2015), and in improving cognitive functions (Harada et al. 2011).

Altogether, the findings confirm that resveratrol might represent a potential benefit for the treatment of inflammation-related neurological or neuropsychiatric diseases, particularly mood-related disorders. However, similar to discussion on curcumin, here also two important points have to be borne in mind. First, because naturally occurring forms of resveratrol have a very limited half-life in plasma, it is important that potent analogs with increased bioavailability be developed. Second, although the effects of resveratrol on neurotrophic and inflammatory mediators are well-established, other mechanisms (e.g., antioxidant, mitochondrial interaction, signal transduction pathways, etc.) may also be involved (Pallàs et al. 2013; Hurley et al. 2014; Lopez et al. 2015).

Concluding Remarks

As mentioned above, to date, a true neuroprotective drug that could substantially prevent the progression of the neurodegenerative diseases is not available. The drugs discussed here have the potential of providing such neuroprotection. In this regard, one's expectation will be to stop or retard the progression of the disease. Moreover, such a drug could be of value in normalizing mood disorders manifested alone or in conjunction with the neurodegenerative disease (see Fig. 3). Although the emphasis in this review has been on inflammatory and neurotrophic involvement, participation of other factors or systems (e.g., oxidative stress, apoptosis/necrosis, mitochondrial damage/repair, etc.) in drug's actions cannot be overruled or ignored. Nonetheless, tapping into such an array of biological

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substrates, one can only hope for development of compounds that can be effective in combating the devastating neuropsychiatric/neurodegenerative diseases.

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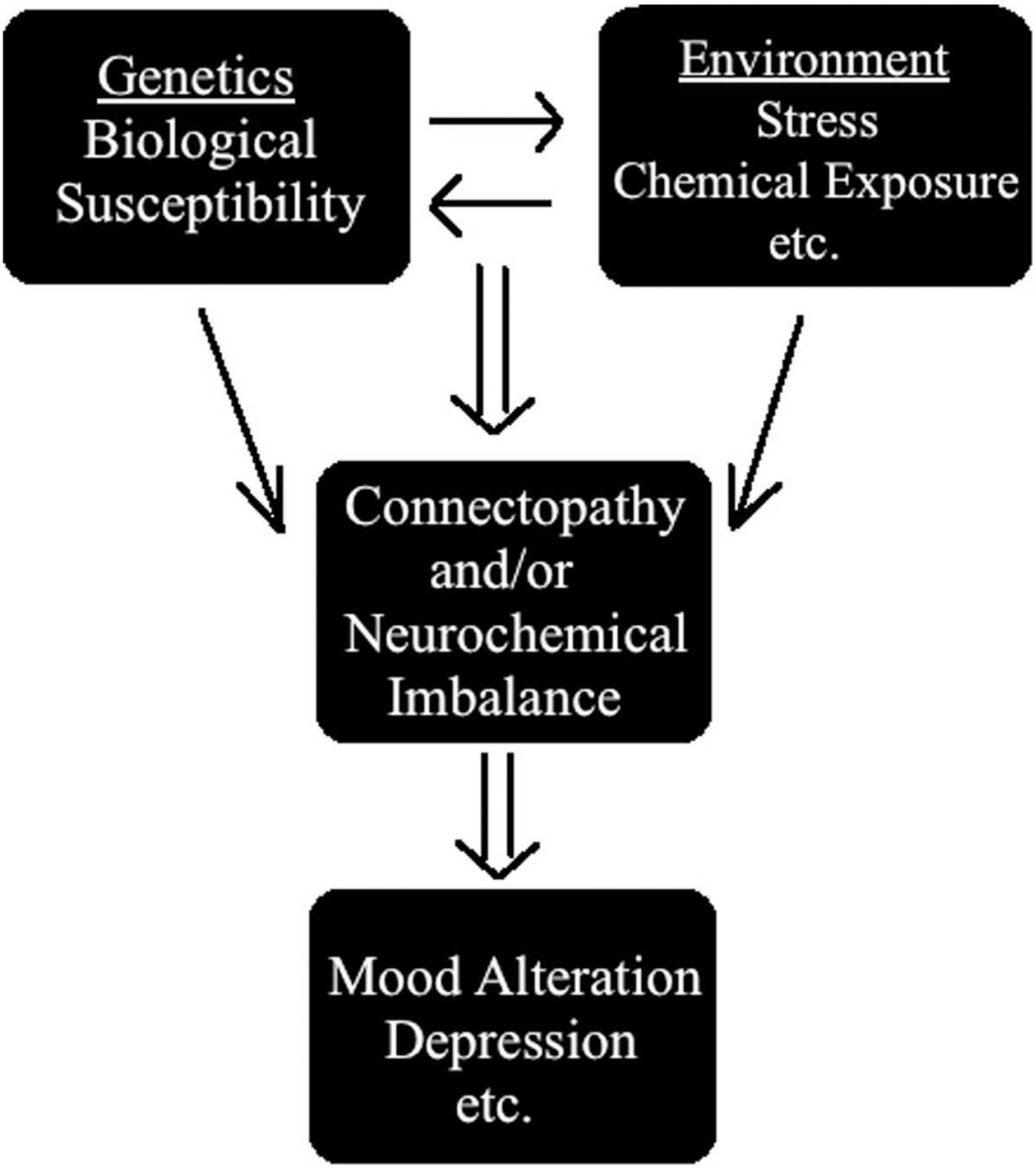

Fig. 1.

Interaction of genetic and environmental factors (particularly stress) can lead to abnormalities in circuit connections (connectopathy) and/or neurochemical imbalance and manifestation of depression

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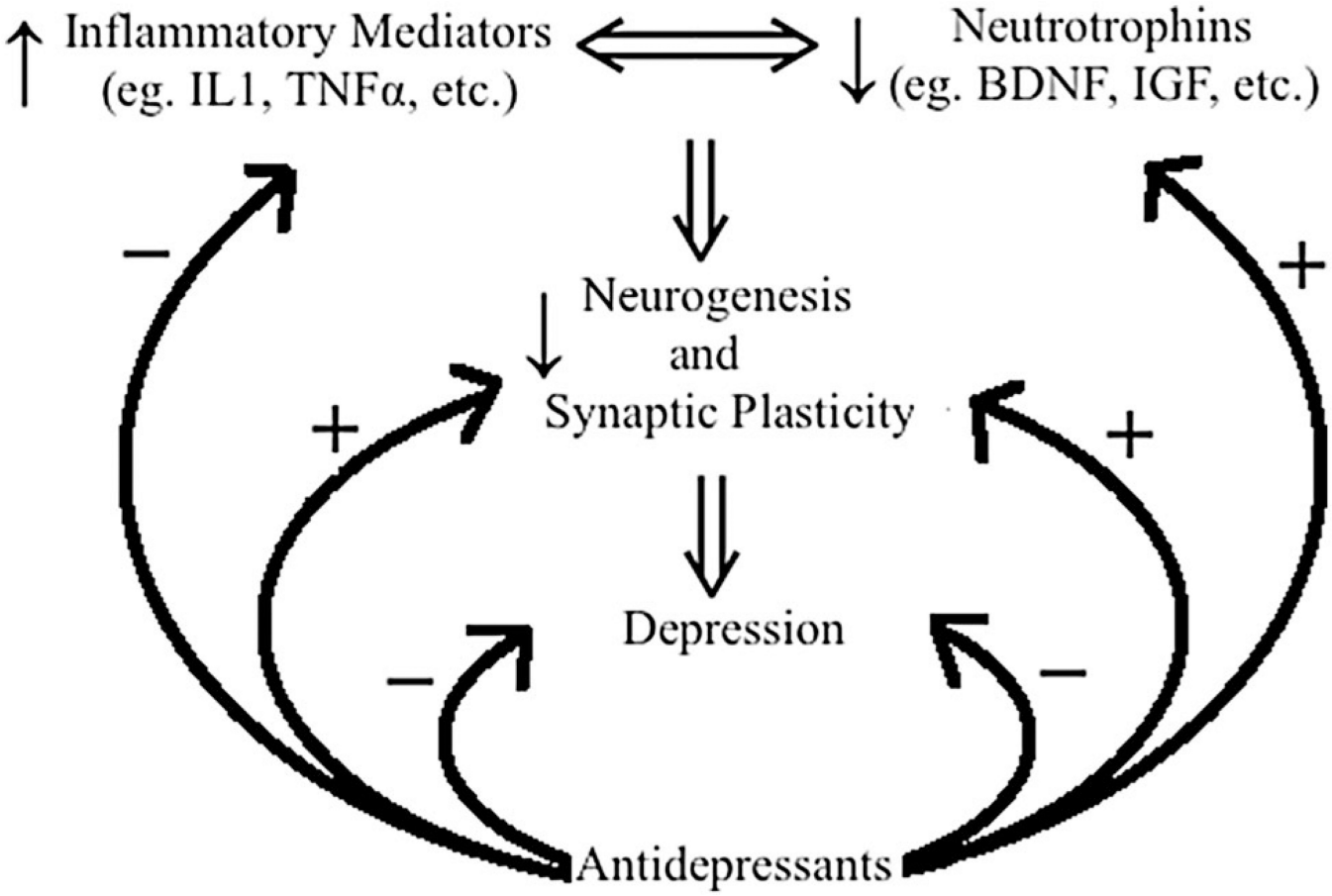

Fig. 2.

Plausible relationship between pro-inflammatory mediators (e.g., cytokines) and neurotrophins (e.g., BDNF and IGF: insulin-like growth factor) in manifestation of depression and reversal by antidepressants

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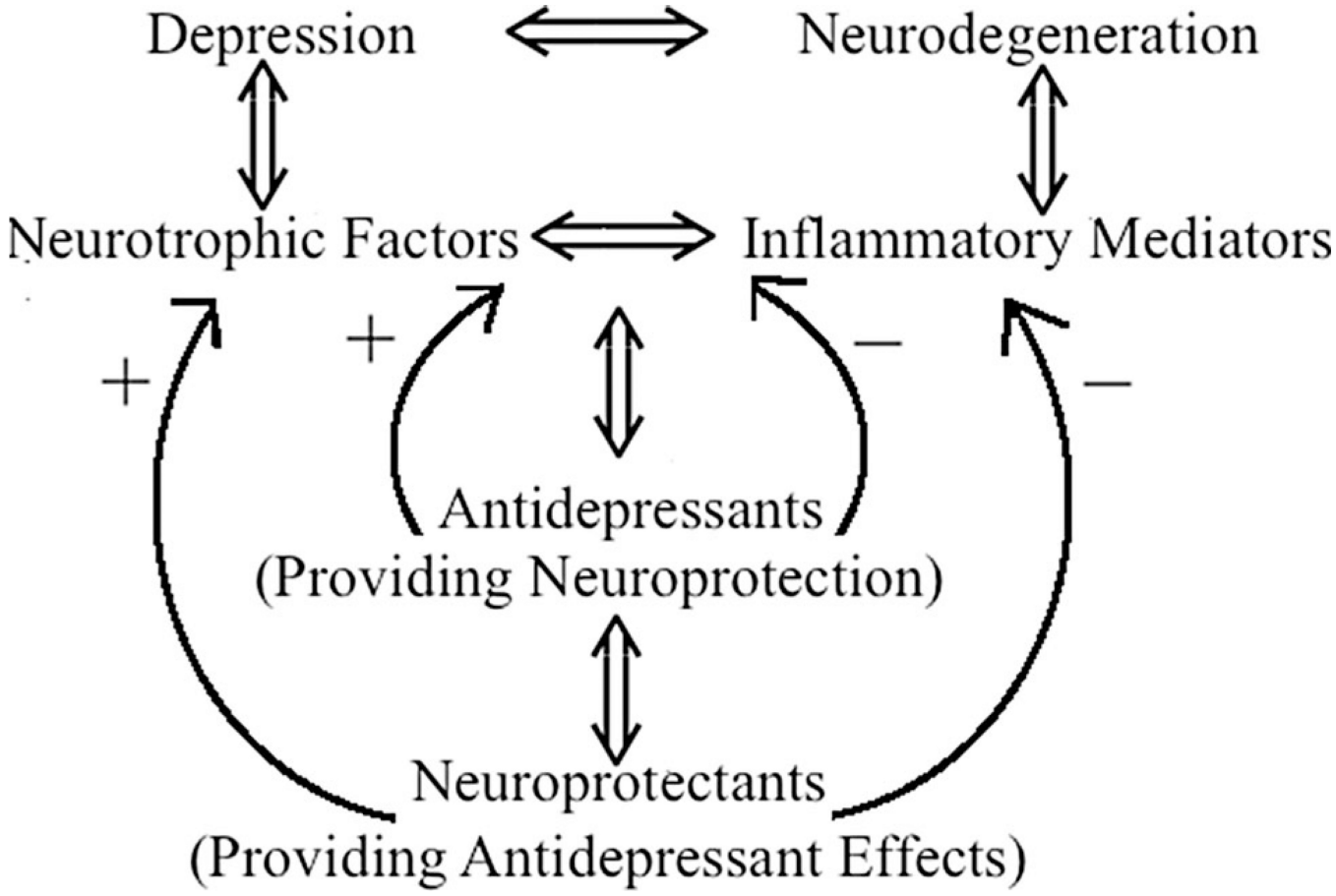

Fig. 3.

Postulated neurobiological commonality involving inflammatory mediators and neurotrophins in depression and neurodegenerative diseases and possible interaction of antidepressants and neuroprotectants with such substrates in providing relief in both conditions

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Table 1

Various classes of currently used antidepressants

Antidepressant class	Drugs
Monoamine oxidase inhibitors (MAOIs)[a]	Isocarboxazid (Marplan), Phenelzine (Nardil), Selegiline (L-Deprenyl, Emsam)
Tetracyclic antidepressants (TetCAs)	Mianserin (Norval), Mirtazapine (Remeron), Amitriptyline (Elavil), Clomipramine (Anafranil)
Tricyclic antidepressants (TCAs)	Imipramine (Tofranil), Desipramine (Norpramin), Nortriptyline (Aventyl)
Norepinephrine dopamine reuptake inhibitors (NDRIs)	Bupropion (Wellbutrin)
Serotonin norepinephrine reuptake inhibitors (SNRIs)	Desvenlafaxine (Pristiq), Duloxetine (Cymbalta)
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine (Prozac), Fluvoxamine (Luvox), Citalopram (Celexa), Escitalopram (Lexapro), Paroxetine (Paxil), Sertraline (Zoloft)

[a]The era of antidepressants was heralded by isoniazid in 1950s, when as an antitubercular agent serendipitously showed euphoric effects in patients with tuberculosis. Probing into the mood elevating property of this drug (MAO inhibition) initiated the synthesis of generations of “biogenic based” antidepressants. Moreover, it indicated a biological basis of the illness (Lopez-Munoz et al. 2007; Ramachandraih et al. 2011)