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Neuroinflammation, Neurodegeneration and Depression

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Abstract

Neurodegeneration and depression are two common co-morbid conditions, particularly within the aging population. Research has linked neuroinflammation as a major contributing factor to both of these diseases. The key to neuroinflammation effects on neurodegeneration and depression appears to lie within the dysregulation of the control and release of pro- and anti-inflammatory cytokines. This can come from an internal or external insult to the system, or from changes in the individual due to aging that culminate in immune dysregulation. The need to reduce neuroinflammation has led to extensive research into neuroprotectants. We discuss the efficacy found with nicotine, alcohol, resveratrol, curcumin, and ketamine. Our main focus will be on what research is telling us about the connections between neuroinflammation, neurodegeneration, and depression, and the hope that neuroprotectants research is giving people suffering from neurodegeneration and depression stemming from neuroinflammation. We will conclude by making suggestions for future research in this area.

1.0 Introduction

The aging baby-boomer population has encouraged an increase in research into age-related neurodegeneration and its causes. This research has led to discoveries that link neuroinflammation to not only neurodegeneration, but also depression. New hypotheses have been developed based on these findings, e.g., the inflammatory and neurodegenerative hypothesis of depression (Maes et al. 2009). However, the lingering question in this regard is the extent neuroinflammation plays in the etiology of neurodegenerative processes and neuropsychiatric disorders such as depression. In this review, we will present arguments in favor of a positive feedback loop between neuroinflammation, neurodegeneration, and depression. To do this we will focus on the relation between depression and neurodegeneration, what neuroinflammation is and its mechanisms, and end with a discussion of research investigating neuroprotectants with an eye towards the neuroinflammation, neurodegeneration, and depression feedback loop (Figure 1). It is important to note that such a review, far from being an exhaustive one, is best envisioned as a framework for further exploration of the interaction between neuroinflammation, neurodegeneration, and depression.

2.0 Depression and Neurodegeneration

Mood disorders, such as depression, are chronic, severe, and often life-threatening illnesses. Although genetic factors likely play a major role in their etiology, research related to anatomical circuitry and biochemical abnormalities underlying their predisposition have shed light into their pathophysiology. Cumulative data indicate that impairments in cellular plasticity underlie the pathophysiology of severe mood disorders (Manji and Duman 2001). However, increasing evidence (discussed below) suggest that neurodegenerative processes,

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reflected in neuronal and glial cell atrophy or loss, may also be contributory factors to mood disorders.

Depression commonly occurs in neurodegenerative diseases such as Alzheimer's disease (de Souza et al. 2010; Raskind 2008; Teng et al. 2008; Zec and Burkett 2008), Parkinson's disease (Gómez-Esteban et al. 2009; Kulisevsky et al. 2008; Simuni and Sethi 2008; Stella et al. 2008), Lewy body disease (Fritze et al. 2011; Takahashi et al. 2009; Yamane et al. 2011), and Huntington's disease (Paulsen et al. 2005; Perlis et al. 2010), but it has been suggested that depression itself, particularly in late life, may be an indication of latent neurodegeneration (Burgut et al. 2006). An association has been seen between late-life depressed mood, anhedonia, apathy, anergia and higher lacunars volume in white matter, suggestive of a role of subcortical ischemic vascular disease in the pathogenesis of such late-life mood disorders (Lavretsky et al. 2008). Additionally, human imaging studies showing cellular loss in key brain regions such as prefrontal cortex and amygdala of patients with mood disorders causally links select reduction in brain volume to depression (Cotter et al. 2001; Rajkowska 2002; Rosso et al. 2005; Sheline et al. 1998). Depending on the region the cause for this reduction may be due to either neurodegeneration or reduction of neurogenesis. For example, there is indication of selective neuronal loss in the paraventricular nucleus of hypothalamus in patients suffering from major depression (Manaye et al. 2005), and depression in human subjects may be associated with a reduction in hippocampal volume (Czeh and Lucassen 2007; Sheline et al. 2003). Animal models of depression support human findings, reporting loss of hippocampal volume or neurodegeneration in selective brain areas. WKY rats, a putative animal model of depression, show reduced hippocampal volume compared to their control, the Wistar rats (Tizabi et al. 2010). They also show reduced number and size of their hypothalamic hypocretinergic neurons, which may underlie the disrupted sleep pattern associated with depressive characteristics in these rats (Allard et al., 2004). On the other hand, it is thought that depression induced by bulbectomy in mice is associated with neuronal loss in areas such as piriform cortex and posterolateral cortical amygdaloid nucleus (Jarosik et al. 2007), or glial cells in the prefrontal cortex (Banasr and Duman 2008).

Depression-associated volume reduction in the hippocampus appears to be more reflective of a reduction in neurogenesis rather than just neuronal atrophy or destruction (Zhao et al. 2008). This contention is further supported by the findings that treatment with antidepressants may promote neurogenesis, and thus normalize the hippocampal volume (Czeh and Lucassen 2007; Sheline et al. 2003). Chronic-mild-stress animal studies suggest that it is reduction in neurogenesis as opposed to a neurodegenerative process in the hippocampus that causes depression in adults (Sapolsky 2004; Toth et al. 2008), but the story is not that simple when considering stress-induced neuroinflammation (Kubera et al. 2011). It is important to note that most animal models of depression induce depression through stress, which in itself may increase the susceptibility of certain neurons to damage or death (McEwen 2008; McKernan et al. 2009). The hypothesis that stress, via activation of neuroendocrine system, neurotransmitter changes and particularly proinflammatory cytokines can induce neurodegeneration and contribute to pathology of depression led to the development of the cytokine hypothesis of depression, which has been consistently tested since the 1990s (e.g., Maes 1993, 1994, 1995, 1999, 2001; Maes et al. 1990, 1995; Qin et al. 2007; Raison et al. 2006; Schiepers et al. 2005; Song and Wang 2011). Stress induced cytokine release is not the only culprit in causing a reduction in neurogenesis. A baseline reduction in hippocampal brain derived neurotrophic factor (BDNF), a marker of neurogenesis, has been observed in WKY rat model of depression, suggestive of a reduced neurogenesis (Hauser et al. 2011). In the interest of brevity, we will primarily discuss neuroinflammation via cytokine function, and will not go in-depth into neuroendocrine and

neurotransmitter involvement. However, we will discuss their roles where appropriate in relation to glial activation of cytokine release.

3.0 Role of Neuroinflammation

Neuroinflammation is defined as the brain's response to injury, infection or disease. The purpose of inflammation in general is to remove or inactivate potentially damaging agents or damaged tissue. This response is primarily mediated via one of two cell systems: glia of the central nervous system (CNS), and lymphocytes, monocytes, and macrophages of the hematopoietic system (Streit et al. 1999; Stoll and Jander 1999). Results of a number of studies suggest that patients who have major depressive disorder show alterations in immunologic markers including increases in proinflammatory cytokine activity and inflammation (Gold and Irwin 2009). Moreover, it has been proposed that chronic low-grade inflammation may result in changes in brain structure and synaptic plasticity leading to neurodegeneration (Hayley et al. 2005; Khairova et al. 2009; Leonard 2007; Maes et al. 2009). Such increases in neurodegeneration, coupled with a reduction in neuroprotection and neuronal repair due to increase in glucocorticoid levels may be the initial pathological markers of depression and a prelude to dementia, particularly in older people (Leonard 2007; Leonard and Myint 2009). Interestingly, neuroinflammation mediated by microglia and astrocytic activation can be suppressed by norepinephrine (NE). Hence, NE uptake inhibitors' therapeutic efficacy in depression may be partially related to NE-mediated anti-inflammatory effects (O'Sullivan et al. 2009). It is of importance to note that chronic stress may exacerbate the release of proinflammatory cytokines and hence precipitate depressive episodes (Maes et al. 2009). It has been shown that stress through its interaction with the immune system may increase the levels of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 (see below). It is now well documented that neuroinflammation is actively involved in neurological diseases and disorders like Alzheimer's disease (Leonard and Myint 2006; Wuwongse et al. (2010), amyotrophic lateral sclerosis, epilepsy, Huntington's disease, multiple sclerosis, and Parkinson's disease (Hemmerle et al. 2012), and that often these diseases show co-morbid expression with depression. Thus, drugs that may interfere with detrimental consequences of stress on inflammatory pathways may offer novel treatments for mood disorders and subsequent neurodegenerative pathologies. Specific pro- and anti- inflammatory mediators will be discussed is more detail below.

4.0 Mechanisms of Neuroinflammation

As mentioned above, glial cells – particularly microglia – are the primary modulators of inflammation in the central nervous system (CNS: Block et al. 2007; Streit et al. 1999; Stoll and Jander 1999). Microglia constantly ‘survey’ their environment and with constitutively expressed surface receptors can trigger or amplify responses to a given insult (Aloisi 2001). Glial activation can be the result of local insult or a response to a systemic insult. However, a key point elaborated below, is that glial cell activation can quickly lead to the release of both pro- and antiinflammatory cytokines. The final effect of cytokine release is dependent on the balance between these opposing responses. In this vein it is postulated that glial activation initially serves a protective function, but that continuous activation can lead to exaggerated release of proinflammatory cytokines and hence neuronal damage. Labeling a given cytokine as pro- or anti-inflammatory can often be misleading, as the response they elicit can vary with exposure duration, target cell and the micro-environment that the cytokines are acting in (Dinarello 1997).

4.1 Cytokines

Cytokines are a large family of small signaling proteins secreted from various cell types that illicit varied biological activity. Key to this review, they induce both an anti- or proinflammatory response within the body. Anti-inflammatory cytokines are generally released to regulate proinflammatory cytokines. This regulation helps limit potentially damaging effects of prolonged or excess inflammation caused by the proinflammatory cytokines. However, dysregulation in cytokines can lead to insufficient mediation or inhibition of normal immune reaction leading to disease manifestation (Dinarello 1997, 1998; Kasai et al. 1997; Munoz et al. 1991; Rubio-Perez and Morillas-Ruiz 2012). For example, IL-1, IL-6, and TNF-α are released in response to disease threat or exotoxins such as lipopolysaccharide (LPS) and typically cause a low-level inflammatory response in order to combat the insult or threat (Barton 1997; Zhang et al. 2012). However, these three cytokines tend to be dualistic in their action. For example, IL-6 has acute proinflammatory action (Hurst et al. 2001; Barton et al. 1996), but can also act to attenuate or down-regulate synthesis of other proinflammatory cytokines (e.g., Interferon-gamma (IFN-γ), IL-1, and TNF-α: Barton 1997; Libert et al. 1994; Xing et al. 1998). Furthermore, it activates release of IL-1 receptor antagonist (IL-1ra) and IL-10, both of which possess potent anti-inflammatory properties (Steensberg et al. 2003).

Similar to IL-6, IL-1 and TNF-α also have acute proinflammatory actions, and dysregulation of production of one or more of these cytokines has been linked to Alzheimer's disease (Swardfager et al. 2010), Parkinson's disease (Nagatsu et al. 2000), cancer (Locksley et al. 2001), inflammatory bowel disease (Brynskov et al. 2002), and major depression (Dowlati et al. 2010; Howren et al. 2009). Furthermore, unregulated IL-1, IL-1β and TNF-α have been shown to impair neurogenesis, exacerbate cell death, and cause neurodegeneration (Goshen et al. 2008; Koo and Duman 2008; Patel et al. 2006; Viviani et al. 2006; Zou and Crews 2005). These effects appear to happen primarily through the cytokines' disruption of survival signaling pathways, caspase-dependant cascades, and alteration of normal receptor function (Patel et al. 2006; Viviani et al. 2006; Zou and Crews 2005). The dysfunction of these cytokines can often be attributed to immune dysregulation (discussed below).

Change in cytokine expression can also occur in the absence of pathology. The expressions of certain cytokines appear to increase as a function of age, suggesting another cause for age related dementia and depression. For example, aging patients without neurological diseases show a progressive increase in the expression of IL-1 and microglia activation (Roubenoff et al. 1998; Wilson et al. 2002), but this increase is still less than in patients with Alzheimer's disease (Griffin et al. 1989). IL-6 levels also increase in the mouse brain with advancing age (Godbout and Johnson 2004), and TNF-α gene expression is dramatically increased in the cerebellum of aged rats compared to young rats (Gemma et al. 2002). Research suggests that immune response-related molecules and their receptors expressed throughout the brain change with age and disrupt normal physiology, contributing to cognitive and behavioral dysfunction (Barrientos et al. 2002, 2010; Lynch 1998, 2002; Pugh et al. 1999, 2001). These changes are possibly due to dysfunction in communication between microglial and neurons caused by “microglial senescence” (Gemma et al. 2010; Streit and Xue 2010).

4.2 Immune dysregulation

The immune system is designed to help protect the body against disease, toxic agents, stress, and injury. Immune response to insult can vary, but inflammation is the first response to infection and injury as the body initiates a defense, mediated by cytokines, followed by the healing process. As discussed above, in a normal functioning system pro- and anti-inflammatory cytokines function in a regulatory loop. However, breakdown of the normal

response by factors such as stress or disease can cause inflammation to become persistent and harmful (Gao and Hong 2008). For example, inflammation induced by LPS – simulating disease induced inflammation – causes long-term increase in TNF-α from brain microglia months after it has subsided in the periphery (Qin et al. 2007). Moreover, this increased proinflammatory response induced a delayed and progressive loss in dopaminergic neurons in the substantia nigra, similar to that seen in Parkinson's disease, suggesting that unregulated neuroinflammation could lead to neurodegeneration (Qin et al. 2007). Similarly, it was demonstrated that IFN-γ induces the enzyme indoleamine 2,3- dioxygenase (IDO), which causes reduction in tryptophan availability, leading to a reduction in serotonin synthesis in the brain (Wirleitner et al. 2003). Since serotonin has been directly implicated in depression and neurodegeneration, this provides further support that unchecked inflammatory response can play a significant role in such disorders.

LPS studies have shown that other proinflammatory cytokines (e.g., IL-6 and IL-1β) can remain elevated and induce symptoms of a syndrome termed “sickness behavior” (Kent et al. 1992; Qin et al. 2007). The symptoms that define sickness behavior vary and bear a strong similarity to depression, including reduction in locomotor activity, anhedonia, anorexia and cognitive disturbances, strengthening the suggestion that the inflammatory response could induce symptoms of depression (Kent et al. 1992; Maes et al. 1993; Yirmiya 1997). In the years since these initial studies, a number of findings have reinforced the idea that unregulated inflammation can lead to depression and possibly neurodegeneration. For example, administration of high levels of proinflammatory cytokines can cause changes in behavior similar to depression and that attenuation of inflammatory response reduces depressive symptoms (Capuron and Miller 2004; Pollak and Yirmiya 2002).

Stress is also known to alter immune functioning. Maes et al. (1998) were the first to show that psychological stress in humans induces an inflammatory response through production of proinflammatory cytokines, such as IFN-γ and TNF-α. Subsequent studies show this to be true in stressful situations as well (Shapira-Lichter et al. 2008; Steptoe et al. 2007). Animal studies also have demonstrated that stressors increase cytokine levels such as IL-1β and IL-6 in the blood and in various brain regions (Goshen et al. 2008; Ishikawa et al. 2001; Nguyen et al. 1998). Goshen et al. (2008) specifically showed that after chronic mild stress normal mice showed increased IL-1β in the hippocampus and depressive-like behavior, but IL-1 receptor deficient mice did not show such behavioral changes. Recently it has been shown that direct administration of TNF-α can also induce a depressive like state that can be blocked with the anti-TNF-α antibody (Kaster et al. 2012). Interestingly, it has been proposed that the action of some antidepressants may also be attributed to a reduction in pro-inflammatory cytokines (Pollak and Yirmiya 2002). For a more detailed review of the role of inflammation in depression see Zunszain et al. (2012).

5.0 Neuroprotectants

Neuroprotectants are drugs that act to protect against or help repair the damaging effects of an insult to the brain. Damage induced by acute disease, trauma or chronic disease (e.g., Alzheimer's and Parkinson's) can lead to cell death through necrosis, apoptosis, or autophagic pathways, some of which can be short term whereas others may cause progressive dysfunction. This variability means that it is unlikely that a single class of neuroprotectant therapy may afford total protection. Neuroprotectants also work through a number of mechanisms some of which may overlap. A major concern with therapeutic interventions is to ensure that targeting a specific pathway would not result in the activation of a compensatory mechanism(s) or increase in activity of one of the other pathways that could undermine the intended purpose (Eisenberg-Lerner et al. 2009; Yokoyama et al. 2008). For example, apoptosis and autophagy interact in several ways: antagonistically, as a

back-up, or in some cooperative manner (see Eisenberg-Lerner et al. 2009). Hence, in some instances protection from apoptosis may lead to an increase in autophagy related cell death (Yokoyama et al. 2008).

Keeping this in mind, there is a lot of hope that regulating neuroinflammation mediated by microglia activation may help prevent or reverse depression and neurodegenerative diseases. A number of drugs have been tested over the years that act on different parts of the inflammatory pathway. Some of the more novel ones including, nicotine, alcohol, resveratrol, curcumin, and ketamine with potential dual application for depression and neurodegeneration will be briefly discussed here.

5.1 Nicotine

Nicotine addiction (from tobacco products) and depression are highly correlated, but the reasons are generally unclear. One possibly is that nicotine demonstrates antidepressant qualities, and often depression relapses when cessation is attempted, leading to “self-medication hypothesis” (Cook et al. 2007; Moreno-Coutiño et al. 2007; Spring et al. 2008). A second possibility is that excessive nicotine use induces depression itself, but this is only consistently seen in adolescence (Parrott 2003; Steuber and Danner 2006; Upadhyaya et al. 2002). Third, nicotine withdrawal induces depression, which likely contributes to the failure rate of smoking cessation (Borrelli et al. 1996; Covey et al. 1997; Edwards and Kendler 2011; Glassman et al. 2001; Tsoh et al. 2000). Preclinical as well as clinical studies suggest an antidepressant-like effect of nicotine. This effect could come from the euphoric effect experienced by new smokers (Pomerleau and Pomerleau 1992). However, it is clear that nicotine (from patch or smoking) has a direct effect in alleviating anhedonia and improving mood in depressed patients (Cook et al. 2007; McClernon et al. 2006; Salin-Pascual et al. 1995). In animal model studies, it is clear that nicotine reduces depressive-like symptoms such as helplessness and anhedonia (Djuric et al. 1999; Kalejaiye et al. 2011, 2012; Semba et al. 1998; Tizabi et al. 1999, 2000, 2009b, 2010). Therefore, depressed individuals may use nicotine as an anti-depressant at first, but continued use may worsen depression during use and withdrawal (Borrelli et al. 1996; Convey et al. 1997; Tsoh et al. 2000; Glassman et al. 2001). This varied relationship between nicotine and depression, may explain the mercurial relationship depressed patients have with nicotine usage (see also reviews by Philip et al. 2010, 2012)

Beyond its anti-depressant qualities, a number of epidemiological and empirical studies also suggest neuroprotective effects nicotine. An inverse relationship between Parkinson's disease and smoking has been consistently demonstrated in epidemiological studies (Baron 1996; Baumann et al. 1980; Dorn 1959; Nefzger et al. 1969; Ross and Petrovitch 2001; Thacker et al. 2007). In-vivo and in-vitro studies have shown that nicotine protects against nigrostriatal damage induced by various compounds. For example, 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; Muñoz et al. 2012; Ramlochansingh et al. 2011), and delays Parkinson's disease-like symptoms induced by MPTP in non-human primates (Quik et al. 2006). Recently it has been suggested that nicotine protection against MPTP in a mouse model of Parkinson's disease is via inhibition of astrocyte activation (Liu et al. 2012). Beyond protection in Parkinson's disease models, nicotine has been seen in in-vitro studies (primary and immortal cell cultures) to protect against or attenuate toxicity induced by LPS, cytokines, glutamate, alcohol, N-methyl-D-aspartate (NMDA) and hypoxia (Dajas-Bailador et al. 2002; Guan et al. 2003; Hejmadi et al. 2003; Kihara et al. 1998; Liu and Zhao 2004; Park et al. 2007; Stevens et al. 2003; Tizabi et al. 2003, 2004, 2005).

The action of this protection is unclear, but it appears to be mediated by activation of multiple nicotinic receptors (Copeland et al. 2005, 2007; Dajas-Bailador et al. 2002; Hejmadi et al. 2003; Picciotto and Zoli 2008; Quik et al. 2009). The signal transduction mechanism(s) underlying the neuroprotection may involve direct or indirect nicotinic receptor mediated modulation of calcium and other anti-apoptotic mechanisms, but the exact mechanism and pathway is still unclear (Donnelly-Roberts et al. 1996; Kihara et al. 2001; Liu and Zhao 2004; Ren et al. 2005; Stevens et al. 2003; reviewed in Buckingham et al. 2009). Regardless of the pathway, it is clear that nicotine or nicotinic agonists may be suitable drugs for treating some neurodegenerative diseases, depression, or both. Important to this review, is that mediation may occur via regulation of neuroinflammation, a contention supported by a number of studies (Cui and Li 2010; Piao et al. 2009; Shi et al. 2009). More specifically, nicotine modulation of innate immune pathway, believed to be primarily mediated by alpha7 nicotinic receptors (Cui and Li 2010), immunosuppressive effects of nicotine (Piao et al. 2009), and attenuation of peripheral as well as central inflammation by nicotine (Piao et al. 2009; Shi et al. 2009) have been reported. Interestingly, vagus nerve modulation of the immune response may also be mediated through alpha7 nicotinic receptors (Ulloa 2005). It remains to be determined however, whether antidepressant effects of vagal stimulation observed in some patients may also be due to inflammatory modulation (Conway et al. 2011; Rizvi et al. 2011).

In addition to neurodegenerative and neuropsychiatric diseases, the anti-inflammatory effects of nicotine may also be applicable to variety of conditions including ulcerative colitis, septic kidney injury and obesity all of which can be precipitated or exacerbated by inflammatory processes (Chatterjee et al. 2012; Lakham and Kirchgessner 2011).

5.2 Alcohol

Depression and alcoholism have a high rate of co-morbidity. There are two primary viewpoints on how these diseases interact: First, chronic alcohol use may result in depressive-like characteristics, which may linger or worsen after cessation (Hodgins et al. 1995; Schulteis et al. 1995). This could be caused by significant interactions of chronic alcohol exposure with neurotransmitter systems that regulate mood (Dixit and Crum 2000; Getachew et al. 2008, 2010; Ratsma et al. 2002; Rozas 2009; Tupala and Tiihonen 2004). Second, depression precedes alcoholism, and may improve at first, but then worsens due to chronic alcohol intake (Dixit and Crum 2000; Rodgers et al. 2000; Spak et al. 2000). We have found that high doses of alcohol induce depressive-like behavior in normal rats and exacerbate that seen in Wistar-Kyoto (WKY) rats which exhibit innate depressive-like behavior (Getachew et al. 2010; Hauser et al. 2011). Moreover, these effects of alcohol can be blocked with prescribed antidepressants (Getachew et al. 2010; Hauser et al. 2011) and nicotine (Kalejaiye et al. 2012). On the other hand, we have also observed antidepressant-like effects of low alcohol doses in WKY rat model of depression (Kalejaiye et al., 2011; Tizabi et al. 2009a). Therefore, it is possible that the initial antidepressant effect of low doses of alcohol may contribute to eventual co-morbidity of alcoholism and depression.

Epidemiological studies show trends that light to moderate drinkers have reduced risk of dementia and cognitive decline in comparison to non-drinkers (reviewed Collins et al. 2009). Furthermore, given in moderate to low doses alcohol provides neuroprotection, this is likely because it dampens the inflammatory processes within the brain or in culture (Belmadani et al. 2001; Collins et al. 2000; Park et al. 2007). Some of these benefits can be attributed to anti-oxidant polyphenols (e.g., resveratrol in red wine: discussed below), but it is likely that alcohol in moderate levels has its own direct neuroprotective effect. Studies have shown that giving low doses of alcohol (ethanol) protects in-vitro and ex-vivo neural cultures exposed to toxins that cause neurodegeneration such as HIV-1 glycoprotein gp120 (gp120: Collins et al. 2000), homoquinolinic acid (Cebere and Liljequist 2003) and NMDA

(Cebere and Liljequist 2003; Chandler et al. 1993; Wegelius and Korpi 1995). Similarly, pre-treatment of SH-SY5Y cells, a cell line commonly used to model nigral dopaminergic neurons for Parkinson's disease with ethanol caused attenuated salsolinol-induced toxicity (Ramlochansingh et al. 2011). The exact neuroprotective mechanism of low alcohol concentration is not known. It appears that several mechanisms may be at work, including alcohol causing increased release of heat shock proteins (Belmadani et al. 2004; Sivaswamy et al. 2010; reviewed in Collins et al. 2010; see also Hurley et al. 2012b). Our preliminary studies in cultured cells indicate protective effects of low alcohol concentrations against LPS and cytokine induced toxicity (Chin et al. 2012; Tizabi et al. 2012b), suggesting a possible anti-inflammatory effect of low alcohol concentration (Chin et al. 2012; Tizabi et al. 2012b). It remains to be determined whether low doses of alcohol could be promoted as neuroprotective or antidepressant based on reduction of neuroinflammation.

5.3 Resveratrol

A natural non-flavonoid polyphenol antioxidant, resveratrol (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. The antidepressant-like effect of resveratrol has been suggested in a preclinical study where it was shown to alleviate depressive-like symptoms in mice (Xu et al. 2010). Although it is unknown how resveratrol antidepressant effect may be mediated, contribution of immune-mediated mechanism (i.e., anti-inflammatory effects) cannot be ruled out. Resveratrol has been shown to impedes cancer progression at various stages (Jang et al. 1997), reduce cardiovascular disease (Bradamante et al. 2004), diminish ischemic injuries (Sinha et al. 2002; Wang et al. 2002), and increase stress resistance while lengthening life (Valenzano et al. 2006). Furthermore, it has been shown in mice that resveratrol improves cognitive functioning by increasing insulin-like growth factor (IGF)-1 (Harada et al. 2011). Neuroprotection by resveratrol is also implied, as it reduces the risk of Alzheimer's (reviewed in Vingtdeux et al. 2008) and Parkinson's disease (Chen et al. 2007; Tredici et al. 1999). Recently, it has been suggested that these effects come from resveratrol mediation of neuroinflammation. Zhang et al. (2012) found that resveratrol significantly inhibited LPS-induced microglial activation, and hence production of TNF-α, IL-1β, and nitric oxide (another proinflammatory factor). Thus, resveratrol might represent a potential benefit for the treatment of inflammation-related neurological or neuropsychiatric diseases, particularly mood related disorders.

5.4 Curcumin

Curcumin, the active ingredient in turmeric (*Curcuma longa*), has been empirically shown to function as an antioxidant (Ruby et al. 1995; Sandur et al. 2007a,b; Sharma 1976), hepato- and nephro-protectant (Kiso et al. 1983; Singh and Sharma 2011; Venkatesan et al. 2000), antimicrobial (De et al. 2009; Wang et al. 2009), anti-inflammatory (Aggarwal and Harikumar 2009; Jurenka 2009), neuroprotectant (Singla and Dhawan 2012), and antidepressant. The antidepressant effects of curcumin have been primarily reported in stress-induced depression models (Bhutani et al. 2009; Kulkarni et al. 2008; Li et al. 2007; Xu et al. 2005a,b). We have recently observed a dose-dependent antidepressant-like effect of curcumin in WKY rats, a non-induced animal model of depression (Hurley et al. 2012a). Curcumin effectiveness against depression has been seen through several pathways. Curcumin increases biogenic amines (e.g., dopamine, serotonin, and norepinephrine) in the cortex and hippocampus after stress and olfactory bulbectomy induced depression-like behavior (Kulkarni et al. 2008; Xu et al. 2005a,b). We have seen an up-regulation of hippocampal BDNF following chronic curcumin treatment (Hurley et al. 2012a). Arora et al. (2011) used curcumin preventatively against pain-induced depression, and found increased biogenic amines. They also found reduction in mRNA and protein of pro-inflammatory cytokines (TNF-α and IL-1β: Abe et al. 1999, Arora et al. 2011) and proteins involved in

apoptotic pathways (NF- κβ and caspase-3: Arora et al. 2011). Thus, multiple mechanisms may be contributing to the antidepressant-like effects of curcumin. However, the mediation of inflammation by curcumin through inhibition of cytokine functions, especially IL-1β and induction of nuclear factor (NF)-κB (Buhrmann et al. 2011) suggests curcumin as a potential multi-target drug to work against depression and neurodegeneration. In regard to neuroprotection, it has been observed that societies that widely use curcumin show reduced incidence of inflammation-influenced and cognitive function diseases (Aggarwal et al. 2007; Chandra et al. 2001; Ng et al. 2006; Vas et al. 2001). Curcumin has also been shown to ameliorate the adverse effects of the mutagenic neurotoxin N-methyl N-nitrosourea in cerebrum and cerebellum of mice (Singla and Dhawan 2012). The potential use of curcumin in neurodegenerative diseases, particularly Alzheimer's and Parkinson's disease has been recently reviewed (Darvesh et al. 2012).

5.5 Ketamine

Ketamine is a non-competitive NMDA receptor antagonist and a derivative of phencyclidine (PCP) that blocks the NMDA receptor (Harrison and Simmonds 1985). Ketamine and other NMDA receptor antagonists have been shown to produce both anxiolytic and antidepressant effects in preclinical studies (Berman et al. 2000; Zarate et al. 2006). Animal studies have borne out this effect: sub-anesthetic dose of ketamine caused an acute and sustained antidepressant-like effect in mice (Maeng et al. 2008) and a single dose of ketamine ameliorated behavioral despair for at least a week after its administration in Wistar rats (Yilmaz et al. 2002). We have also reported that administration of low ketamine doses lead to reduced depressive-like behavior as assessed in the forced swimming test while increasing AMPA/NMDA receptor density ratio in the hippocampus of WKY rats (Tizabi et al. 2012a). Clinical studies have shown significant reduction of depressive symptoms within 72 hours of ketamine administration (Berman et al. 2000; Zarate et al. 2006), 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).

Ketamine has also been shown to prevent endotoxin (Escherichia coli) induced-shock in rats by inhibiting release of plasma cytokines such as TNF-α and IL-6 and reducing inflammation (Taniguchi et al. 2001, 2004). LPS-induced expression of proinflammatory cytokines such as TNF-α, IL-6, iNOS, NF-κB, and activator protein (AP)-1 is also attenuated by ketamine, without effecting expression of anti-inflammatory cytokines like IL-10 (Helmer et al. 2003a,b). In-vitro, ketamine blocked LPS-induced IL-1β and IL-6 at low doses and TNF-α at higher dose due to inhibition of extracellular signal-regulated kinase (ERK1/2) phosphorylation (Chang et al. 2009). It is unknown if ketamine anti-inflammatory effect may be linked to its antidepressant effect, or if it may be an effective neuroprotectant. Preliminary studies do not support protection against apoptotic neurodegeneration (Ribeiro et al. 2012). On the contrary ketamine may cause neurodegeneration in the developing brain (Soriano et al. 2010; Zou et al. 2009; reviewed by Schifilliti et al. 2010). However, a critical consideration in these studies is the dose of ketamine used, as too high of a dose can cause addiction or toxicity. Future studies incorporating low ketamine doses could shed light on possible neuroprotectant effect of ketamine. Moreover, establishing the exact interaction of ketamine with inflammatory system and its possible application in depressive as well as neurodegenerative disorders remain to be determined.

6.0 Future considerations

Study of neurodegeneration and depression has revealed a common thread of neuroinflammation as a major contributing factor to their manifestation. There is hope in curbing the cycle of neuroinflammation, neurodegeneration, and depression through the use

of neuroprotectants that act on that link (Fig 1). As we have discussed in this review, there is a lot of promise in neuroprotectants, especially naturally derived ones, that act to regulate cytokine release and reduce neuroinflammation and depression, while also blocking the neurodegenerative process. There is even more hope, as it is found that combining natural anti-inflammatories (e.g., curcumin and resveratrol) produce a multilevel mediation of inflammation, and therefore provide more chance of interfering with manifestation of neurodegeneration and/or depression (Csaki et al. 2009; Van der Schyf 2011). Nonetheless, the full story of how neuroinflammation, neurodegeneration and depression are linked and regulated remains to be elucidated. Therefore, future research needs to closely scrutinize these intriguing relationships particularly in reference to any novel intervention or pharmacotherapy.

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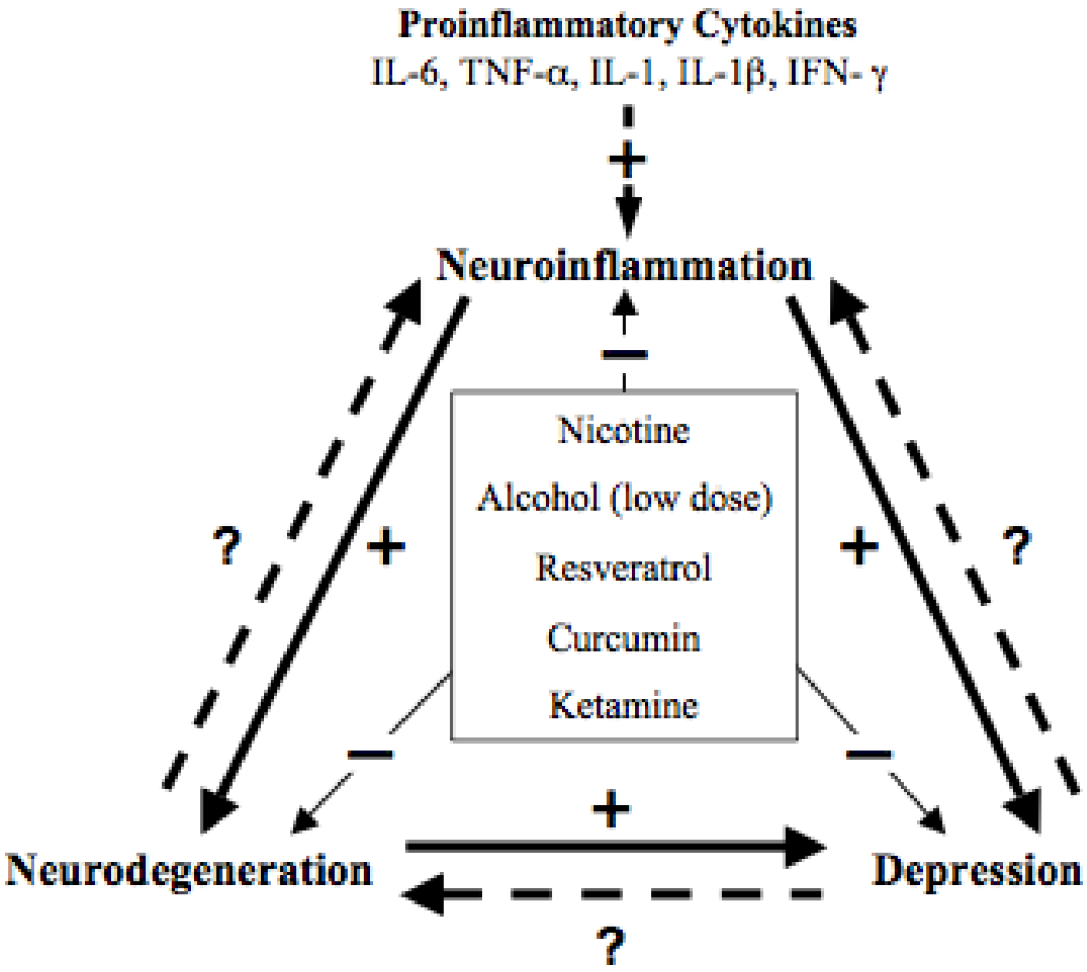

Figure 1.
The cycle of neuroinflammation, neurodegeneration, and depression, including alterations by key neuroprotectants. Solid line with: (+) indicates a positive influence, (−) denotes inhibition or alleviation of inflammatory response, neurodegeneration and depression. Dashed line with (?) is an unknown or un-established effect.