



The putative neurodegenerative links between depression and Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the leading neurodegenerative cause of dementia in the elderly. Thus far, there is no curative treatment for this devastating condition, thereby creating significant social and medical burdens. AD is characterized by progressive cognitive decline along with various neuropsychiatric symptoms, including depression and psychosis.

Depression is a common psychiatric disorder affecting individuals across the life span. Although the "monoamine hypothesis" of depression has long been proposed, the pathologies and mechanisms for depressive disorders remain only partially understood. Pharmacotherapies targeting the monoaminergic pathways have been the mainstay in treating depression. Additional therapeutic approaches focusing other pathological mechanisms of depression are currently being explored.

Interestingly, a number of proposed mechanisms for depression appear to be similar to those implicated in neurodegenerative diseases, including AD. For example, diminishing neurotrophic factors and neuroinflammation observed in depression are found to be associated with the development of AD. This article first provides a concise review of AD and depression, then discusses the putative links between the two neuropsychiatric conditions.

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Abbreviations: 5HTT, serotonin transporter; A β , amyloid beta; ACh, acetylcholine; AChE-I, acetylcholinesterase inhibitor; ACTH, adrenocorticotropic hormone; AD, Alzheimer's disease; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate; APP, amyloid precursor protein; BACE1, β -site APP cleaving enzyme; BDNF, brain derived neurotrophic factor; BuChE, butyrylcholinesterase; CREB, cAMP response element binding protein; CRH, corticotropin releasing hormone; GSK-3 β , glycogen synthase kinase-3 beta; HPA, hypothalamus-pituitary-adrenal; IDO, indoleamine-pyrrole 2,3-dioxygenase; IFN γ , interferon gamma; IFN α , interferon alpha; IL-1 β , interleukin 1 beta; IL-6, interleukin 6; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; MAOI, monoamine oxidase inhibitor; MAPK, mitogen activated protein kinase; MDD, major depressive disorder; NFT, neurofibrillary tangles; NGF, nerve growth factor; NMDA, N-methyl-D-aspartic acid; NF κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PD, Parkinson's disease; PS1, presenilin 1; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TLR, toll-like receptor; TNF α , tumor necrosis factor alpha; TGF β , transforming growth factor beta.

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1. Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative form of dementia. Aging is the most important risk factor for AD. The prevalence of AD is approximately 7–10% in individuals over the age of 65 and increases to about 40% over the age of 80. AD is incurable and increases the mortality rate by approximately 40% in men and women. The number of people who have AD is expected to double every 20 years, thereby constituting significant medio- and socio-economical burdens (Alzheimer's Association, 2009).

Several genetic risk factors have been identified in AD. Mutations in the amyloid precursor protein (APP) gene on chromosome 21, presenilin 1 (PS1) on chromosome 14, and presenilin 2 on chromosome 1 have been found to be responsible for the early-onset, autosomal dominant forms of AD (Levy-Lahad et al., 1995; St George-Hyslop et al., 1987; Van Broeckhoven et al., 1992). Alternatively, the epsilon 4 variant of apolipoprotein E gene located on chromosome 19 has been found to be involved in the late-onset, sporadic form of the disease (Utermann, 1994). These genetic factors influence the pathology of AD by enhancing the accumulation and aggregation of amyloid β ($A\beta$) and neurofibrillary tangles (NFT) (Selkoe, 2001; Williamson et al., 2009). Other important candidate genes include death associated protein kinase 1—an enzyme involved in neuronal apoptosis; insulin-degrading enzyme gene responsible for producing insulin degrading enzyme, which is involved in the degradation and clearance of $A\beta$; and growth factor receptor-bound 2 associated binding protein, which was found to be overexpressed in pathologically vulnerable neurons and its expression increases tau hyperphosphorylation (Bertram et al., 2000; Li et al., 2006; Reiman et al., 2007). More recently, the neuronal sortilin-related receptor gene on chromosome 11, has been shown in several studies to be associated with AD (Rogaeva et al., 2007; Webster et al., 2008).

1.1. Clinical and pathological features of AD

The primary clinical presentation of AD is progressive cognitive decline, with memory loss being a relatively early sign of the disease. AD patients also have problems in language, recognition, and executive functioning. Besides cognitive deficits, patients frequently exhibit a number of neuropsychiatric symptoms including depression, anxiety, and psychosis (Garcia-Alberca et al., 2008). The behavioral and psychological symptoms may worsen the disability and caregiver burden (Starkstein et al., 2008).

The AD brain shows prominent atrophic changes in the hippocampal, frontal, parietal, and temporal areas (Wenk, 2003). Such changes are secondary to massive neuronal death and synaptic degeneration (DeKosky and Scheff, 1990).

$A\beta$ plaques and NFT are the most prominent histological features in the AD brain. NFT are positively associated with clinical severity in AD patients, estimated by the Clinical Dementia Rating and Mini-Mental State Examination scores (Giannakopoulos et al., 2003; Gold et al., 2001). On the other hand, studies regarding the clinical correlations of $A\beta$ plaques are equivocal (Gold et al., 2001). $A\beta$ and NFT trigger a number of mechanisms leading to neuronal death. Altered cholinergic and glutamatergic neurotransmission, apoptosis, oxidative stress, calcium homeostasis dysfunction, and neuroinflammation are some of the proposed mechanisms implicated in the AD pathogenesis.

1.1.1. Pathogenic factors for AD

$A\beta$ is believed to play a central role in the pathogenesis of AD. Extracellular $A\beta$ plaques found in AD brains are surrounded by dystrophic dendrites and axons, activated microglia, and reactive astrocytes (Gomez-Isla et al., 2008).

$A\beta$ is an abnormal by-product of the cleavage of APP. APP is a transmembrane protein having roles in neuronal protection and development (Turner et al., 2003). APP is cleaved by α , β , and γ -secretases. APP can undergo two cleavage pathways: amyloidogenic and non-amyloidogenic, depending on the cleaving enzymes involved. When APP is cleaved by α -secretase followed by γ -secretase, the possibility of $A\beta$ formation is eliminated, as α -secretase mediated cleavage occurs within the $A\beta$ region (Sisodia, 1992). Under the "amyloidogenic" condition, APP is first cleaved by β -secretase followed by the γ -secretase cleavage, thereby releasing the neurotoxic 40 to 42 amino acid peptidic fragments. β -site APP cleaving enzyme 1 (BACE1) and presenilins have been suggested to be the major constituents of β - and γ -secretases, respectively (Hampel and Shen, 2009; Thinakaran et al., 1996; Vassar, 2004). Recent studies show that oligomeric $A\beta$ are also neurotoxic. These findings suggest that $A\beta$ -mediated neurotoxicity could be an early pathological event leading to neuronal demise in AD (Pereira et al., 2005; Schott et al., 2006).

Intraneuronal NFT are composed of hyperphosphorylated tau proteins (Glennner and Wong, 1984). Tau is a microtubule-associated protein in neurons with the function of maintaining microtubule stability. Hyperphosphorylation of tau results in the self assembly of "pair helical filaments", thereby compromising microtubule stability, neuronal viability, and the eventual formation of NFT (Iqbal et al., 1986). In the AD brain, glycogen synthase kinase-3 β (GSK-3 β) and cyclin-dependent kinase 5 have been shown to be associated with NFT formation (Ishiguro et al., 1991; Ishiguro et al., 1993). The accumulation of $A\beta$ appears to activate these proteins to trigger pathological tau processing (Gotz et al., 2001).

1.1.2. From cholinergic neurons to glutamatergic neurons in AD

Multiple neurotransmitter systems have been reported to be altered in the AD brain. Significant pyramidal neuronal loss result in diminished acetylcholine (ACh), epinephrine, and serotonin transmissions in the cortex and hippocampus, accounting for the symptoms in AD (Perry et al., 1999). Loss of cholinergic neurons and their respective cortical projections to the forebrain have been widely studied with respect to AD-associated cognitive deficits. In AD brain, reduction of muscarinic and nicotinic cholinergic receptor activities and decreased levels of ACh have consistently been demonstrated (Fisher, 2008; Nordberg and Winblad, 1986). Severe cholinergic deficit observed in the AD basal forebrain has been studied extensively and has been regarded as arguably the most important neurotransmitter system involved in AD pathogenesis; however, more recent research focuses on the important interplay between neurotransmitter systems, rather than solely on the cholinergic system.

Overstimulation of excitatory amino acid receptors would lead to excessive intracellular calcium, triggering an excitotoxic cascade resulting in neuronal demise (Nicholls and Budd, 1998; Olney, 1969). For example, calcium overload activates protein kinase C, phospholipases, proteases, protein phosphatases, and nitric oxide synthases. Excessive activation of these enzymes has been shown to cause damage to the cell membrane, cytoskeleton, or DNA (Choi, 1988; Dawson et al., 1992; Law et al., 2001; Trout et al., 1993).

Glutamate is the most abundant excitatory neurotransmitter for cortical and hippocampal pyramidal neurons, playing important roles in cognition and memory (Fonnum, 1984; Francis et al., 1993). Alterations of glutamate transporters and receptors have been observed in AD brain (Francis et al., 1993). Activation of N-methyl-D-aspartic acid (NMDA) receptors has been implicated in A β -mediated excitatory neurodegeneration and NMDA receptor antagonists could be neuroprotective (Parsons et al., 2007; Snyder et al., 2005).

1.1.3. Neurodegenerative processes in AD

Mitochondria are responsible for cellular energy production. Inhibition of the electron transport chain in mitochondria results in the imbalanced production of free radical species, leading to oxidative stress, and ultimately neuronal damage (Nakabeppu et al., 2007). α -Ketoglutarate dehydrogenase complex, pyruvate dehydrogenase complex, and cytochrome oxidase – rate-limiting enzymes in the mitochondrial respiratory chain and are responsible for reducing molecular oxygen – have consistently been shown to be involved in mitochondria dysfunction in AD (Gibson et al., 1988; Kish et al., 1992; Sorbi et al., 1983).

Increase in oxidative stress and impaired antioxidant mechanisms have been observed in AD brains (Smith et al., 1996). Advanced glycation end products, nitration, and lipid peroxidation adduction products have been shown to be involved in neuronal damage (Good et al., 1996; Sayre et al., 1997; Smith et al., 1994). Moreover, activities of antioxidant enzymes – e.g. copper/zinc superoxide dismutase – are significantly reduced (Marcus et al., 1998).

Apoptosis is hypothesized to account for, at least in part, the neuronal loss observed in AD. The presence of activated caspases, altered expressions of apoptotic-related genes, and DNA fragmentation are observed in the AD brain (Gorman, 2008). In the triple transgenic AD mice model and AD brains, A β accumulation triggers caspase activation, thereby leading to caspase-mediated tau cleavage. These are considered to be early events that precede NFT formation and cognitive decline in AD (Rissman et al., 2004). Furthermore, A β can induce apoptosis by increasing intracellular calcium and oxidative stress (Eckert et al., 2003). Studies show activation of stress kinases – c-Jun N-terminal kinase, p38, protein

kinase R and its downstream kinase eukaryotic initiation factor 2 α – in AD neuronal apoptosis (Chang et al., 2002; Suen et al., 2003; Zhu et al., 2001, 2000). It has been reported in several studies that intraneuronal A β may also induce neuronal apoptosis (Chui et al., 1999; Hayes et al., 2002; Ohyagi et al., 2005).

Autophagy is a cellular mechanism for lysosomal degradation of cytoplasmic content. Increasing lines of evidence support the role of autophagy in AD pathogenesis. Disruption of endosomal-lysosomal system has been observed in AD and is suggested to precede the formation of plaques and tangles (Cataldo et al., 2000). Pathological accumulation of autophagic vacuole has been observed in dystrophic neuritis (Yu et al., 2005). Upregulation of the autophagy-lysosomal degradation pathway leading to increased production and accumulation of intracellular A β have been observed in AD (Billings et al., 2005).

Synaptic degeneration was found to be an early event in AD which correlates well with cognitive dysfunction (DeKosky et al., 1996; Selkoe, 2002). Synaptic degeneration is reflected by reduction in synaptic vesicle proteins required for vesicle trafficking, docking, fusion to the synaptic membrane, and neurotransmitter exocytosis. These vesicular proteins include synaptotagmin and synaptosomal-associated protein of 25 kDa which are involved in the transport of proteins from neuronal cell bodies to axonal terminals (Davidsson et al., 1996; Dessi et al., 1997). Reduction in pre-synaptic and post-synaptic proteins including synaptophysin, synaptotagmin, and synaptopodin has been observed in AD patients (Masliah et al., 2001; Reddy et al., 2005). On the other hand, increase in the postsynaptic density-associated protein of 95 kDa (PSD-95) has been observed in post-mortem AD brains which could be secondary to compensatory mechanisms (Leuba et al., 2008). Furthermore, soluble oligomeric A β appears to be involved in synaptic failure (Haass and Selkoe, 2007).

Impaired adult neurogenesis has been observed in several neurodegenerative diseases including AD. Deficient neurogenesis was found in the forebrain of the PS1 knockout mouse model of AD (Feng et al., 2001). Studies have shown neurogenesis impairment in AD mouse models. For example, in the PDAPP mouse model, decreased neurogenesis was observed to be responsible for age-related cognitive deficits (Donovan et al., 2006). Furthermore, the Tg2576 transgenic mice showed reduced cell proliferation in the dentate gyrus and contextual memory deficits (Dong et al., 2004).

There is also evidence of ongoing inflammatory processes in AD. A β has been found to activate immune response. Microglia are major cells of immune responses in the central nervous system (CNS) and they have been found to phagocytose and degrade A β (Blasko and Grubeck-Loebenstein, 2003). However, overstimulation of activated microglia surrounding the A β deposits has been found to induce toxicity through inflammatory mediators (Akama and Van Eldik, 2000). Microglia interact with A β through cell surface complex receptors including CD36, CD37, and integrin (Bamberger et al., 2003). Activated microglia induces pro-inflammatory cytokines such as tumor necrosis factor α (TNF α), interferon γ (IFN γ), interleukin 1 β (IL-1 β) and interleukin 6 (IL-6), which have been found to produce neurotoxic free radicals (Akama and Van Eldik, 2000).

1.2. Treatment of AD

The treatment of AD thus far relies on symptomatic relief. The first drugs to be approved for the symptomatic treatment of AD are the acetylcholinesterase inhibitors (AChE-I). Since the reduction in cholinergic neurons has been observed in AD brains, effort has been made to increase cholinergic activity in the brain. Studies have shown that they are able to improve cognition in AD patients (Birks, 2006).

1.2.1. Current available treatments

AChE-I drugs are considered as first-line treatments for AD in some countries. Donepezil, rivastigmine, and galantamine are prescribed to patients diagnosed with AD (Birks, 2006). Rivastigmine also acts as an inhibitor of butyrylcholinesterase (BuChE) – another enzyme that degrades acetylcholine in the synapse (Giacobini et al., 2002).

Memantine is a non-competitive, moderate- to low affinity NMDA receptor antagonist, recommended for the treatment of moderate to severe AD. It has been found to protect neurons from glutamate-mediated toxicity (Reisberg et al., 2003). Memantine is able to delay the development of agitation and aggression and other neuropsychiatric symptoms (Danysz and Parsons, 2003).

1.2.2. Therapeutic research directions

Apart from symptomatic treatment, there has been an increase in the development of disease-modifying therapeutic approaches over the years, mainly focusing on amyloid production and toxicity in AD.

GSK-3 β plays a pivotal role in the pathogenesis of AD including increasing tau hyperphosphorylation and A β production. Hence, agents that inhibit GSK-3 β have shown potential in the treatment of AD. Lithium was the first GSK-3 β inhibitor to be discovered. However, due to its non-specificity, it can be neurotoxic (Klein and Melton, 1996). At present, the specific GSK-3 β inhibitor NP031112 is in clinical trials for treatment of AD (Martinez and Perez, 2008).

Proteases involved in the cleavage of APP to A β have been put forward as potential disease-modifying drug targets. Increased expression of BACE1 results in the increase formation of A β (Hampel and Shen, 2009). A BACE inhibitor, TAK-070, has been shown to reduce A β and subsequent plaque formation in the cerebral cortex *in vivo* (Miyamoto et al., 2001). Other potential approaches include upregulation of α -secretase or stimulating this pathway to promote the non-amyloidogenic pathway of APP processing and inhibition of γ -secretase to lower A β production (Lanz et al., 2003; Postina et al., 2004). Cu²⁺/Zn²⁺ chelators have also been found to inhibit the aggregation of A β (Cherny et al., 2001; Postina et al., 2004). Moreover, report has shown that treatment which can maintain A β in its soluble form is able to prevent cell death in neuronal cultures and inhibit amyloid deposition (Gervais et al., 2007).

A combination of synthetic A β 42 AN1792 and the adjuvant QS-21 is under clinical development as active immunization for AD (Bayer et al., 2005). Preclinical studies suggested the benefit of AN1792 in lowering A β levels; however, there have been safety concerns regarding encephalitis (Bayer et al., 2005; Orgogozo et al., 2003). Passive immunization approaches have also been investigated. Peripherally administered antibodies were found to be effective in reducing AD pathology in transgenic mice models. LY2062430 is in phase II while Rinat RN-1219/PF-0436036 is in phase I clinical trial for passive immunization against AD (DeMattos et al., 2001; Wilcock et al., 2004). However, passive immunization is highly selective, limiting its efficacy. Bapineuzumab has moved to phase III trial and data from these studies will provide useful information on the efficacy of passive immunization in AD immunotherapy (Nitsch and Hock, 2008).

Other targets apart from A β have also been investigated as potential treatment for AD. Earlier studies revealed significant reduction in muscarinic and nicotinic receptor density in AD brains (Whitehouse et al., 1986). Clinically, the muscarinic receptor antagonist scopolamine is found to elicit amnesia (Renner et al., 2005). This provides the platform for the development of muscarinic receptor agonists. Recent developments of selective allosteric muscarinic agonists have been found to achieve higher therapeutic index and fewer adverse side-effects (Fisher, 2008).

At present, the nicotinic compounds ABT-089 and TC-1734 are in phase II clinical trials for AD (Parikh et al., 2008). Positive modulators of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, IDRA-21, CX-516 and S18986-1 are showing promising therapeutic effects. These compounds have been shown to improve cognitive decline, attention, and memory (Buccafusco et al., 2004; Dicou et al., 2003; Hampson et al., 1998).

Latrepidine has received a significant amount of attention due to its ability to improve cognitive impairment in AD patients (Doody et al., 2008). It was originally developed as a nonselective antihistamine. Latrepirdine has been shown to block NMDA receptors, stabilize neuronal Ca²⁺ homeostasis and mitochondrial function (Bachurin et al., 2001). However, in animal models of AD, latrepirdine has been shown to increase the level of extracellular A β (Steele et al., 2009). Several trials are ongoing to confirm its efficacy and safety.

Nerve growth factor (NGF) has also been shown potential as a therapeutic agent for AD, as it appears to have neurotrophic effects on the basal forebrain cholinergic neurons. NGF delivery has been a challenge since NGF does not readily cross the blood brain barrier and NGF treatment is accompanied by several adverse side-effects (Cattaneo et al., 2008). A promising approach of using NGF is through gene therapy. *In vivo* NGF gene delivery into the brain using the Adeno-Associate Virus vector system has been found to be beneficial in animal models and is now under phase I clinical studies (Bishop et al., 2008). Studies have also investigated the intranasal and ocular administration of NGF. Both routes have been shown to ameliorate neurodegeneration and behavioral deficits in transgenic mice (Capsoni et al., 2009). Furthermore, brain-derived neurotrophic factor (BDNF) gene delivery has also been shown to have neuroprotective effects in rodent and primate models of AD (Nagahara et al., 2009).

Development of disease-modifying agents for AD is beginning to shift from a single-target to a multiple-target therapy. AD and other neurodegenerative diseases often involve multiple processes. Therefore, a single agent that can target several disease mechanisms could be beneficial. Currently, ladostigil, a novel drug that inhibits acetylcholinesterase, BuChE, and MOA-A and B, is in phase II clinical trials for AD (Bolognesi et al., 2009).

2. Depression

Major Depressive Disorder (MDD) is a neuropsychiatric syndrome consisting of having low mood, anhedonia, along with somatic and cognitive disturbances. Depression affects over 120 million people worldwide and is predicted to be the second leading cause of disability after heart disease by the year 2020 (Murray and Lopez, 1997).

2.1. Clinical and pathological features of depression

A number of genetic risk factors involved in the etiology of depression have been identified. Genes responsible for regulation of monoamines, corticotropin releasing hormone (CRH), and BDNF were found to be altered in depression. For example, mutations in monoamine oxidase A (MAO-A), catechol-methyltransferase, and serotonin transporter (5-HTT) genes resulted in psychiatric disturbances, including depressive behaviors (Haavik et al., 2008; Jabbi et al., 2008; Savitz and Drevets, 2009). Other risk factors that are consistently linked to depression include female gender, adverse environmental factors such as stressful life events, adverse childhood experiences and certain personality traits (Kendler et al., 2004).

Brain imaging and post-mortem studies of depressed patients show decreases in grey-matter volume and glial density in the prefrontal cortex and hippocampus, which are the regions

implicated in the cognitive aspects of depression (Czeh and Lucassen, 2007). However, studies have failed to show reduction in hippocampus volume as the disease progresses. Follow up studies of depressed patients showed no hippocampal and amygdala differences between patients and healthy controls during the follow-up period. Nonetheless, patients with smaller hippocampal volumes and a previous history of depression had a worse clinical outcome (Frodl et al., 2008, 2004), thereby suggesting hippocampal volume reduction could be a predisposing factor, rather than a characteristic of the disease.

2.1.1. HPA axis dysregulation

A consistent finding in patients with depression is elevated levels of the stress hormone cortisol (Yu et al., 2008). Patients with Cushing's syndrome – a state of hypercortisolaemia – frequently present depressive symptoms (Gillespie and Nemeroff, 2005). The hypothalamic–pituitary–adrenal (HPA) axis is intimately involved in stress response and the regulation of various physiological processes. The hypothalamus secretes CRH and vasopressin which activates the pituitary to secrete adreno-corticotrophic hormone (ACTH). ACTH stimulates the adrenal gland to secrete glucocorticoids, with cortisol being the primary glucocorticoid in humans (Swaab et al., 2005).

The glucocorticoid receptor regulates the HPA axis and decreased receptor sensitivity has been shown in depressed patients (Pariante, 2004). Inhibition of glucocorticoid receptor has been found to alleviate depressive symptoms and antidepressant treatment could reduce glucocorticoid levels (DeBattista and Belanoff, 2006). Thus far, study results on the relationship between HPA axis dysfunction and cognitive impairment have been inconsistent (Bremmer et al., 2007; O'Brien et al., 2004). Differences in the methodology and experimental factors may contribute to the observed discrepancy.

2.1.2. Dysregulation of monoaminergic neurotransmitters

The earliest mechanism found to be involved in the etiology of depression is the dysregulation of monoaminergic neurotransmitters. The “monoamine theory” originated from early clinical observations in the 1950s that monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA) were able to lift mood in depressed patients by increasing levels of serotonin or norepinephrine (Crane, 1956; Kuhn, 1958).

Serotonin and norepinephrine are neurotransmitters primarily involved in regulation of mood and emotions (Butler and Meegan, 2008). Alterations in serotonergic transmission occur in the CNS of patients with MDD (Owens and Nemeroff, 1994). Neuroimaging studies of patients with MDD showed abnormalities in serotonergic transmission (Staley et al., 1998). Reduced norepinephrine transmissions from the locus coeruleus and caudal raphe nuclei has also been observed in depression (Leonard, 1997). Regulations of serotonergic and norepinephrine circuits are known to indirectly modulate the dopamine system, which is implicated in anhedonia (Dunlop and Nemeroff, 2007).

2.1.3. Involvement of inflammation and neurotrophic factor deficiency in depression

Neuroinflammation has recently been suggested to play important role in the etiology of depression. Activation of the immune system has been observed in a number of depressed patients (Muller and Schwarz, 2007). Depressive disorders are often observed in patients with immunologically-related diseases (Bruce, 2008). Furthermore, individuals who have undergone immunotherapy using interferon α (IFN α) in the treatment of cancer and hepatitis C develop depressive symptoms (Wichers et al., 2005). Immune activating agents such as vaccines or endotoxin treatment have been shown to result in depressive

symptoms when administered to healthy adults (Wright et al., 2005).

Several cytokines are able to activate HPA axis (Muller and Schwarz, 2007). Furthermore, hyperactivated HPA axis promotes the release of cytokines from macrophages, exacerbating the cortisol release (Dantzer et al., 2008). Cytokines are also able to influence the serotonergic and norepinephrine systems, which have been observed in depressed patients (Tsao et al., 2006). The precise mechanism of cytokine involvement in depression is unclear. Activation of the NF κ B pathway peripherally and centrally by cytokines is thought to result in reduced monoamine production, reduced neurotrophic factors, and increased excitotoxicity (Dantzer et al., 2008).

Current clinical and experimental evidence strongly suggest indoleamine-pyrrole 2,3-dioxygenase (IDO) are involved in cytokine-induced depression. IDO is an enzyme that degrades tryptophan which is an essential amino acid for the production of serotonin; hence, pathogenic IDO activation could result in reduced serotonin synthesis. Reduction in tryptophan level is also accompanied by increased levels of kynurenine, which generates neurotoxins – 3-hydroxykynurenine and quinolinic acid – and stimulates hippocampal NMDA-receptors, which could eventually lead to neuronal death (Wichers et al., 2005). Several cytokines have been found to be associated with the activation of IDO. Acute activation of IFN γ by toll-like receptor (TLR)-4 or TLR-2 activates IDO peripherally and centrally in mice. Chronic activation of the immune system results in a sustained high levels of IFN γ and the subsequent activation of IDO (Moreau et al., 2005). Increased levels of TNF α have been found to activate adrenergic autoreceptors, leading to a reduction of norepinephrine and trigger depressive symptoms (Reynolds et al., 2005). Recent findings have also demonstrated that inhibition of pro-inflammatory cytokine-mediated signaling results in antidepressant-like effects. IL-6 knockout mice showed resistance to depressive symptoms induced by stress, while TNF α receptors knockout mice show antidepressant-like response (Simen et al., 2006).

Neurotrophic factors have been found to be important in the etiology of depression. Reduction in hippocampal volume has been observed in depression and has been found to be associated with lowered levels of neurotrophic factors (Czeh and Lucassen, 2007). They can regulate neuroplasticity in the adult brain, which has been implicated in the molecular mechanism antidepressants (Thompson, 2002).

Several neurotrophic factors have been identified to promote neurogenesis. A neurotrophic factor highly implicated in depression is BDNF. Postmortem hippocampus of depressed patients and serum of depressed patients show a reduction in BDNF (Monteggia et al., 2004).

Several animal studies have demonstrated that stress exposure reduces BDNF-mediated signaling in the hippocampus (Duman and Monteggia, 2006; Kuroda and McEwen, 1998). BDNF-mediated signaling is involved in neuroplastic responses to stress and antidepressants. Chronic treatment with antidepressants has been found to increase BDNF-mediated signaling (Siuciak et al., 1997). Experiments in rodents show that infusion of BDNF into the hippocampus produced antidepressant-like effects while genetic knockout of the gene encoding BDNF blocked the effects (Nagahara et al., 2009).

BDNF binds to the TrkB receptor, activating intracellular signaling cascades including the mitogen activated protein kinase (MAPK) pathway to phosphorylate cAMP response element binding protein (CREB) (Kozisek et al., 2008). CREB is a transcription factor and appears to be involved in the pathogenesis of depression by controlling neuroplasticity (Carlezon et al., 2005). CREB has been found to be upregulated by chronic antidepressant treatment in several studies, and high levels of CREB had

antidepressant-like effects in animal models (Blendy, 2006; Thome et al., 2000).

2.2. Antidepressants

2.2.1. Existing depression pharmacotherapy

It has been first observed that iproniazid – a MAOI – used in the treatment of tuberculosis, showed antidepressant effects (Crane, 1956). Similar effects were observed with imipramine – a TCA – which was under trials as an antihistamine (Kuhn, 1958). Hence, the monoaminergic system became the key target for antidepressant development. MAOI and TCA inhibit reuptake and prevent the breakdown of monoamines, thereby increasing synaptic concentration. Enhanced monoaminergic neurotransmission is believed to alleviate depression.

MAO-A metabolizes serotonin, norepinephrine, and dopamine. It is thought to be the main enzyme that lowers monoamine levels in depression (Meyer et al., 2006). MAOI such as iproniazid and phenelzine are able to increase the levels of monoamines by preventing their breakdown. However, they are problematic due to numerous serious hepatotoxic side-effects (West and Dally, 1959).

TCA binds non-selectively to serotonin and norepinephrine transporters resulting in the inhibition of the reuptake process. Although they are non-selective, amitriptyline and imipramine are slightly more potent inhibitors of norepinephrine than serotonin (Frazer, 1997). Studies show that they are effective in improving depressive symptoms compared to placebo (Klerman and Cole, 1965). However, TCA also binds to muscarinic, cholinergic, histamine, and adrenergic receptors, producing undesirable and potentially life-threatening side-effects (Richelson, 1994; Tollefson, 1991).

Following the development of TCA and MAOI, selective serotonin reuptake inhibitors (SSRI) were subsequently developed. SSRIs are selective inhibitors of serotonin transporter protein. Owing to its selectivity, they exhibit fewer side-effects than TCA and MAOI. SSRIs are currently recommended as the first-line treatment for depression. Recently developed antidepressants targeting both the serotonergic and noradrenergic system have been found to exhibit higher efficacy (Holliday and Benfield, 1995).

Different therapeutic interventions that elevate levels of monoamines alleviate depressive symptoms; however, the exact mechanism of action remains unclear. Immediate elevated levels of monoamines are observed after SSRI administration, yet two to six weeks are often required for mood-lifting effects (Thompson, 2002; Whyte et al., 2004). This suggests long-term adaptations in neurotransmitter systems are likely required.

Increased levels of serotonin and norepinephrine by SSRI activate the G-protein seven transmembrane domain receptors. This increases cAMP production, cAMP-dependant protein kinase activation, and phosphorylation of target proteins – one of which being the transcription factor CREB. Activation of serotonin receptors phosphorylates CREB through the Ca²⁺/calmodulin-dependent kinases and MAPK signaling pathways (Mattson et al., 2004).

Animal studies have shown that adult neurogenesis is required for antidepressants to be effective (Czeh and Lucassen, 2007; Santarelli et al., 2003). Studies have shown increased adult neurogenesis after antidepressant treatments in rats (Malberg et al., 2000). Decrease in hippocampal neurogenesis has been found to be alleviated or reversed after administration of antidepressants (Alonso et al., 2004; van der Hart et al., 2002). Antidepressants have also been reported to increase survival of the newly generated neurons (Nakagawa et al., 2002). Levels of BDNF mRNA in cortical and hippocampal regions have been shown to be elevated following chronic antidepressant drug administration in rats (Monteggia et al., 2004).

2.2.2. Antidepressant research directions

Agents targeting non-catecholamine neurotransmitter systems are under investigation as potential antidepressants. The “glutamate modulating approach” emerged from evidence that antidepressants have effects on specific glutamate receptor subtypes (Manji et al., 2003). These include NMDA receptor antagonist, metabotropic glutamate receptor agonists, and modulators of AMPA receptors (Mathew et al., 2008). Studies show that riluzole – an NMDA receptor antagonist used to treat amyotrophic lateral sclerosis – could be beneficial in the treatment of depression (Zarate et al., 2003). AMPA and NMDA neurotransmission mediates neuroplasticity of limbic and reward circuits implicated in mood disorders including depression (Schloesser et al., 2008).

Neuropeptides are short-chain amino acids that act as neurotransmitters and regulate mood and anxiety. Stress-related neuropeptides have been recognized as potential targets for treatment of depression. CRH antagonists and neurokinin receptor antagonists are two classes of neuropeptides that are in phase II and III randomized control trials for the treatment of depression, respectively (Mathew et al., 2008).

3. Depression and Alzheimer's disease

3.1. Epidemiological observations

As mentioned earlier, AD patients often exhibit psychiatric symptoms along with cognitive decline. The high prevalence rates for psychiatric disturbance in AD subjects were observed in separate studies (Burns et al., 1990; Lyketsos et al., 2000b). Depression and apathy were amongst the most common manifestations associated with AD (Lee and Lyketsos, 2003). A cross-sectional study of psychiatric symptoms in 435 AD patients demonstrate high rates of depression and showed that it was one of the earliest neuropsychiatric abnormalities to develop (Craig et al., 2005).

A number of risk factors for depression in AD patients have been identified: family history of mood disorder in first-degree relatives, past history of depression, female gender, and early onset AD (Butt and Strauss, 2001; Lyketsos and Olin, 2002). A history of depression itself has also been associated with increased risk of developing AD, especially among elderly women (Green et al., 2003; Lyketsos and Olin, 2002).

Anxiety and depression have been shown to increase the severity of cognitive decline in AD patients (Starkstein et al., 2008). AD patients with depression have lower quality of life, increased levels of disability in performing daily activities, and greater caregiver burdens (Gonzalez-Salvador et al., 1999, 2000; Lyketsos et al., 1999). Depression in AD has also been associated with higher mortality and suicidal rate (Rovner et al., 1991). Hence, the comorbidity of depression and AD is a significant clinical concern (Table 1).

3.2. Genetic studies

Several genetic factors have been identified to influence the development of depression and AD. Genetic polymorphism of the pro-inflammatory cytokine IL-1 β has been found to be involved in depression and AD. AD patients that are heterozygous for a polymorphism in the promoter region of IL-1 β are at high risk of developing depression compared to individuals that were homozygous for the genetic variant (McCulley et al., 2004).

BDNF genetic variation has been found to play a role in the susceptibility to depression and AD. A common single nucleotide polymorphism in the BDNF gene substitutes valine into methionine (Val66Met) which affects the intracellular packing and activity dependent secretion of BDNF. This results in altered

Table 1
Similarities and differences in inflammatory factors, neurotrophic factors and apoptotic markers between depression and Alzheimer's disease.

	Depression	Alzheimer's disease
Pro-inflammatory		
IL-6	<p><i>Animal studies</i> IL-6 knockout mice results in depressive behaviors (Simen et al., 2006)</p> <p><i>Human studies</i> ↑ Levels in depressed patients (Pace et al., 2006; Kim et al., 2007; Bremmer et al., 2007)</p>	<p><i>Animal studies</i> ↑ Immunostaining in AD mouse model and is associated with amyloid deposition (Ruan et al., 2009)</p> <p><i>Human studies</i> ↑ Upregulated in AD brains (Sokolova et al., 2009) ↑ Gene expression in cultured human brain endothelial cells treated with Aβ (Vukic et al., 2009) ↑ Monocyte-derived dendritic cells from AD patients produced higher amount of IL-6 cells (Ciaramella et al., 2009)</p>
IL-1 β	<p><i>Animal studies</i> IL-1β results in depressive behaviors in nerve injury mouse model (Norman et al., 2009)</p> <p><i>Human studies</i> ↑ Levels in depressed patients (Song et al., 2009)</p>	<p><i>Animal studies</i> ↑ Immunostaining in AD mouse model and is associated with amyloid deposition (Ruan et al., 2009)</p> <p><i>Human studies</i> ↑ Gene expression in cultured human brain endothelial cells treated with Aβ (Vukic et al., 2009)</p>
TNF α	<p><i>Animal studies</i> TNFα receptors knockout mice showed antidepressant-like response after stress (Simen et al., 2006)</p> <p><i>Human studies</i> ↑ Levels in depressed patients (Kim et al., 2007; Sutcgil et al., 2007) ↑ Receptor numbers in depressed patients (Grassi-Oliveira et al., 2009)</p>	<p><i>Animal studies</i> ↑ Immunostaining in AD mouse model and is associated with amyloid deposition (Ruan et al., 2009)</p> <p><i>Human studies</i> ↑ Levels in AD patients (Guerreiro et al., 2007)</p>
IL-12	<p><i>Human studies</i> ↑ Levels in depressed patients (Kim et al., 2002; Sutcgil et al., 2007)</p>	<p><i>Human studies</i> ↑ Levels in AD patients (Guerreiro et al., 2007)</p>
IFN γ	<p><i>Human studies</i> ↓ Levels in depressed patients (Song et al., 2009)</p>	<p><i>Human studies</i> CSF levels remain unchanged in AD patients (Rota et al., 2006) ↑ Peripheral levels in AD patients (Reale et al., 2008)</p>
Anti-inflammatory		
IL-10	<p><i>Human studies</i> ↓ Levels in depressed patients (Song et al., 2009)</p>	<p><i>Human studies</i> Levels of protein and gene expression did not appear to be related to AD (Culpan et al., 2006) CSF levels remain unchanged in AD patients (Rota et al., 2006)</p>
IL-4	<p><i>Human studies</i> ↑ Levels in patients with depressive disorder (Kim et al., 2007; Song et al., 2009) ↓ Levels in patients with depressive disorder (Sutcgil et al., 2007)</p>	<p><i>Human studies</i> ↓ Peripheral levels in AD patients (Reale et al., 2008)</p>
Neurotrophic factors		
BDNF	<p><i>Animal studies</i> ↓ Decreased hippocampal BDNF in mouse model of major depression (Knapman et al., 2009)</p> <p><i>Human studies</i> ↓ Post-mortem depressed patient brains and serum of depressed patients (Monteggia et al., 2004) ↓ Serum concentrations and mRNA in depressed patients (Hellweg et al., 2008)</p>	<p><i>Animal studies</i> ↓ Levels in transgenic mouse model of AD and is dependent on amyloid aggregation state (Peng et al., 2009)</p> <p><i>Human studies</i> Gene polymorphism in AD patients (Matsushita et al., 2005) ↓ Levels in CSF of AD patients (Li et al., 2009) ↓ Levels in serum of AD patients (Laske et al., 2007)</p>
NGF	<p><i>Animal studies</i> ↓ Expression of NGF in olfactory bulbectomized rat model of depression (Song et al., 2009)</p> <p><i>Human studies</i> ↓ Serum concentrations in depressed patients (Hellweg et al., 2008)</p>	<p><i>Animal studies</i> Aβ induces NGF dysmetabolism in transgenic AD model (Bruno et al., 2009)</p> <p><i>Human studies</i> ↓ Immunostaining in post-mortem AD brains (Hefti and Mash, 1989)</p>
VGF	<p><i>Animal studies</i> Anti-depressant effects in mouse model of depression (Thakker-Varia et al., 2007)</p>	<p><i>Human studies</i> ↓ Levels in CSF of AD patients (Selle et al., 2005)</p>
Apoptosis		
Pro-apoptotic markers	<p><i>Animal studies</i> ↑ Cleaved PARP and damage of monoaminergic neurons in light deprivation model of depression (Gonzalez and Aston-Jones, 2008)</p> <p><i>Human studies</i> ↑ Caspase 9 activity in post mortem brains of depressed patients (Harlan et al., 2006)</p>	<p>For evidence of apoptotic markers in AD, see review (Gorman, 2008)</p>
Anti-apoptotic markers	<p><i>Animal studies</i> ↓ Bcl-2 in restraint stress model of depression (Luo et al., 2004) ↓ pAkt in social defeat model (Krishnan et al., 2008)</p> <p><i>Human studies</i> ↓ ERK activity in post mortem brains of depressed patients (Dwivedi et al., 2001)</p>	<p>For evidence of apoptotic markers in AD, see review (Gorman, 2008)</p>

hippocampal morphology, affecting mood and memory (Borroni et al., 2009).

These genetic studies have provided evidence on the likely relationship between depression and AD. Interestingly, depression and AD appear to share common neuropathological processes. Nonetheless, the precise mechanisms remain unclear.

3.3. Pathological and biochemical linkage

Neuronal death plays an important role in the pathogenesis of AD. Although massive loss in neurons has not been observed in depression, several studies have shown an increase in pro-apoptotic markers and a decrease in anti-apoptotic markers in animal models of depression (Bachis et al., 2008; Luo et al., 2004). Postmortem brains of depressed subjects also show reduced levels of extracellular signal-related kinase 1/2 which are responsible for neuroplasticity and cell survival (Dwivedi et al., 2001).

Neurodegeneration in AD brain leads to decreased monoamines levels in the hippocampus, locus coeruleus, and brainstem raphe nucleus, all of which are regions implicated in the pathogenesis of depression (Weinshenker, 2008). Neurodegeneration in AD brain may also disturb CRH signaling (Meynen et al., 2007). On the other hand, high levels of CRH and cortisol, secondary to HPA axis deregulation, are known to increase the risk of AD development (Murialdo et al., 2000).

Neurotrophic factors are necessary for neuronal survival. Reduction in neurotrophic factors results in reduced neurogenesis and impairment of neuroplasticity. Neurogenesis and neuroplasticity play major roles in the development of depression and also the molecular mechanisms of antidepressant drugs. In AD, disruption in the neurotrophic factor BDNF signaling has been shown to promote the amyloidogenic pathway in hippocampal neurons, subsequently leading to the activation of apoptosis (Matrone et al., 2008). BDNF has also been found to exhibit neuroprotective properties in several animal models of AD. In the amyloid transgenic mice, BDNF gene delivery can reverse synaptic loss, partially normalize aberrant gene expression, improve cell signaling, and restore cognitive functioning (Saura et al., 2004). In adult rats and primates, BDNF can prevent lesion-induced death of entorhinal cortical neurons and reverse neuronal atrophy, and ameliorate age-related cognitive impairment in aged primates (Nagahara et al., 2009).

Increase in pro-inflammatory cytokines has also been observed in both depression and AD. Pro-inflammatory cytokines influence neuronal functioning in brain regions associated with both depression and AD, namely the prefrontal cortex and hippocampus (Leonard and Myint, 2006). Significant increases in producing cytokines (IL-1 β , IL-6, IL-12, and TNF α) by monocytes have been found in patients with AD and mild cognitive impairment (Guerreiro et al., 2007). These pro-inflammatory cytokines have been reported to modulate central neurotransmitters and growth factors, which is highly implicated in depression and is associated with the severity of the disease (Dantzer et al., 2008). In particular, IL-1 β has been found to impair BDNF signaling in AD models (Tong et al., 2008). Pro-inflammatory cytokines also induce the production of oxidative species and other neurodegenerative factors (Leonard and Myint, 2006).

In conjunction with the increase in pro-inflammatory cytokines, reductions in anti-inflammatory cytokines have also been observed in depression and AD. Studies have shown reduced levels of IL-4 and IL-10 in depressed patients. On the other hand, AD patients demonstrate elevated anti-inflammatory response compared to age-matched controls (Richartz-Salzbunger et al., 2007). However, in contrast to the protein levels, a study has shown that the level of IL-10 gene expression was not related to AD (Culpan et al., 2006). Reduced levels of anti-inflammatory cytokines, IL-4 and IL-10, have been demonstrated in animal models of AD (Michelucci et al., 2009; Song et al., 2009). Hence, the roles of anti-inflammatory factors are still unclear.

Inflammation can result in several consequences including dysregulation of the HPA-axis, production of oxidative species, and activation of IDO and tryptophan-kynurenine pathway. The production of oxidative species and the neurotoxic by-products of the tryptophan-kynurenine pathway (such as 3-hydroxykynurenine and quinolinic acid) have been shown to result in neurodegeneration.

Suranyi-Cadotte et al. have shown that platelet ^3H -imipramine binding is reduced in depressed but not AD patients. This study suggests that ^3H -imipramine binding could be a useful laboratory index to differentiate between patients with major depression and AD. However, a reduction in CNS or platelet serotonergic function was found to be reduced in both depression and AD, suggesting the putative involvement of the serotonergic system for the two conditions (Suranyi-Cadotte et al., 1985). Serotonin has been found

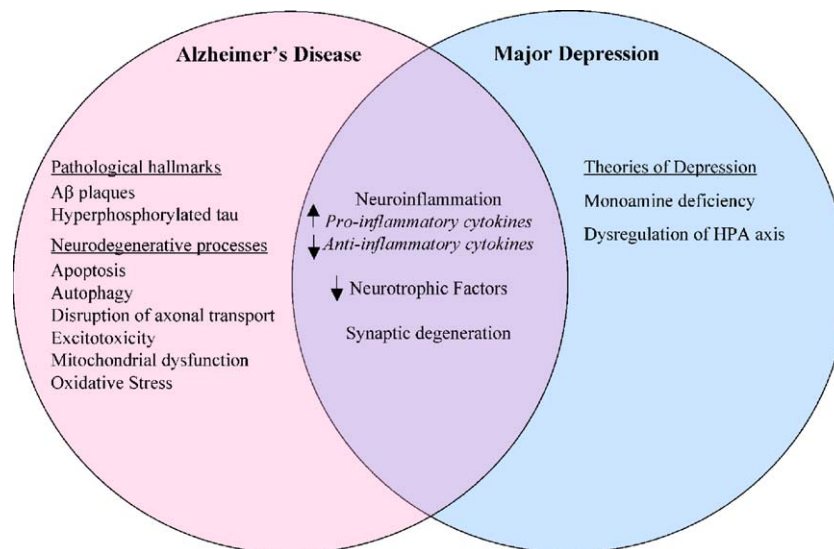


Fig. 1. Current understanding on the common factors shared between depression and AD. AD is pathologically characterized by A β plaques and NFT which results in neurodegeneration via several mechanisms including excitotoxicity and mitochondrial dysfunction. Depression on the other hand is characterized by monoamine deficiency and HPA-axis dysregulation. These two conditions appear to share common factors including inflammation and reduction in neurotrophic support.

to modulate learning and memory (Gonzalez-Burgos and Fera-Velasco, 2008). Antidepressants targeting the monoamines have been studied as potential remedies for AD. Fluoxetine and setraline have been shown to improve cognition in AD patients (Lyketos et al., 2000a; Mossello et al., 2008). Multifunctional drugs are agents with more than one therapeutic mechanism. Ladostigil, a multifunctional drug, has also shown potential for the treatment of both depression and dementia (Poltyrev et al., 2005; Youdim and Buccafusco, 2005). Animal studies also show improvement of depression and AD related pathologies after paroxetine or fluoxetine administration (Nelson et al., 2007; O'Leary et al., 2009). These studies provide evidence to support the role of antidepressants in the treatment of both disorders and the putative linkage between AD and depression.

3.4. Clinical investigation

Besides AD, depression is thought to precede other neurological conditions including stroke and Parkinson's disease (PD). A large number of studies have already shown the subsequent development of depression following stroke (Fedoroff et al., 1991; Robinson and Price, 1982). Interestingly, recent epidemiological studies are beginning to demonstrate that depression may lead to stroke (Larson et al., 2001; May et al., 2002). Furthermore, 40% to 50% of PD patients suffer from depression (Cummings, 1992; Dooneief et al., 1992). Depression is thought to precede the PD motor symptoms in a number of patients (Taylor et al., 1986). Moreover, a recent study has demonstrated the association between Lewy body dementia in patients and late-onset depression (Kobayashi et al., 2009). Thus far, several lines of evidence have indicated the putative links between depression and neurodegenerative diseases, and that depression could be an early symptom of neurodegeneration (Amieva et al., 2008).

The evidence from the preceding paragraphs mostly point toward positive associations between neurodegenerative disorders and depression. These seemingly suggestive findings, however, could not indicate any causality between these conditions at the cellular or clinical level. A neurodegenerative process – depending on the anatomy and pathophysiology involved – could lead to the development of depression is a conceivable notion. Thus far, there is no convincing evidence to implicate depression as a cause of neurodegeneration. While a number of pro-inflammatory markers are increased in both depression and AD, these observations do not necessarily imply that the two conditions are linked, as they could simply be coincidental findings. Moreover, neuropsychiatric disorders may share similar pathological mechanisms; the currently available data are insufficient to support a unique association between depression and AD per se.

While cellular and animal studies can provide important information regarding disease mechanisms, cautious interpretations must be exercised as findings from these experiments may not be relevant to human. Furthermore, even positive findings from biochemical and pathological studies using human subjects may not be clinically significant. From a clinical perspective, depression is indeed a frequent comorbidity in AD patients; nonetheless, a significant portion of individuals afflicted with AD do not have coexisting depression. Lindsay et al did not find a significant association between history of depression and AD (Lindsay et al., 2002). Studies have also shown no association between HPA axis function and AD, while others show no correlation between cortisol levels and memory impairment in AD patients (Souza-Talarico et al., 2009; Swanwick et al., 1998). Although depression has been described to be a risk factor for AD, the emergence of depressed mood as the initial manifestation – preceding noticeable cognitive difficulties – of an underlying neurodegenerative process could also be a distinct possibility. This

is a reasonable consideration because neuropathologies are usually present during the “asymptomatic” period – from a cognitive standpoint – of an individual who would eventually be diagnosed with AD. While there have been multiple studies indicating a positive link between depression and AD, the possibility of publication bias should not be ignored.

The “vascular depression hypothesis” has been proposed in response to the increased likelihood of developing depression in patients with cardiovascular abnormalities, including coronary artery disease, diabetes, and stroke (Alexopoulos et al., 1997). While the indication that depression could cause a cerebrovascular event is questionable, this serves as an interesting reminder regarding the intimate relationship between the cardiovascular and neurological systems. Cardiovascular dysfunction has increasingly been recognized as a significant risk factor for dementia (Whitmer et al., 2005). The possibility of vascular abnormality being the ultimate common denominator for the development of

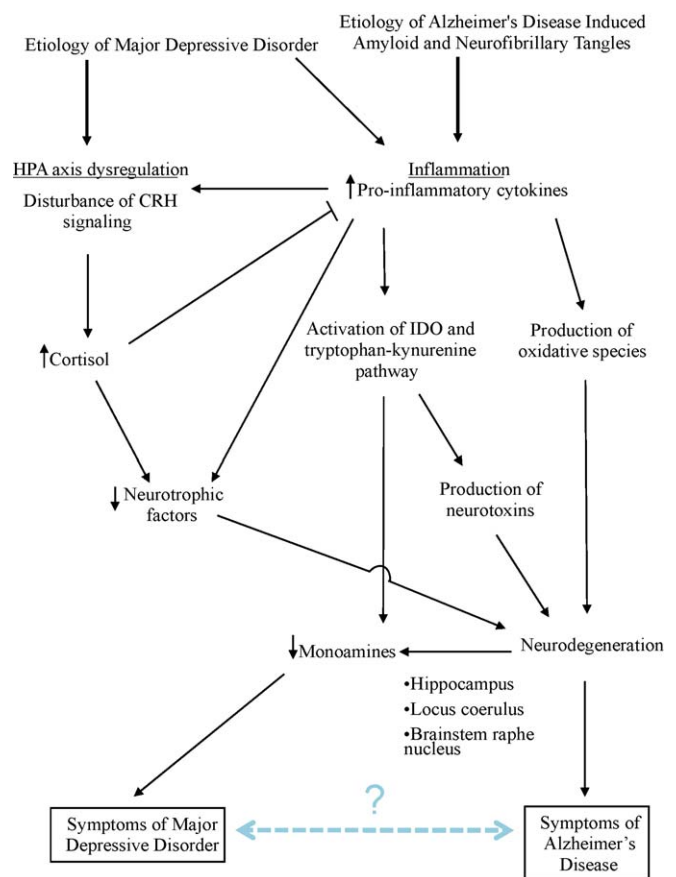


Fig. 2. Schematic diagram demonstrating the putative neurobiological processes underlying the development of depression and AD. Dysregulation of the HPA axis, inflammation, reduction in monoamines and neurotrophic factors are observed in Major Depressive Disorder. Activation of the HPA axis stimulates the release of cortisol, which has a negative impact on the immune system. However, hypersecretion of cortisol due to HPA axis dysregulation results in receptor desensitization, impairing the negative feedback on the immune system. This leads to the release of pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF α . Increase in cortisol and production of pro-inflammatory cytokines results in the reduced level of BDNF. Inflammation itself can also cause dysregulation of the HPA axis, as well as the production of oxidative species and activation of IDO and tryptophan-kynurenine pathway. The production of oxidative species and the neurotoxic by-products of the tryptophan-kynurenine pathway (such as 3-hydroxykynurenine and quinolinic acid) lead to neurodegeneration. Activation of the tryptophan-kynurenine pathway is also responsible for the decreased level of monoamines. Decreased levels of monoamines can also be due to the degeneration of monoaminergic neurons in the hippocampus, locus coeruleus and brainstem raphe nuclei.

various neuropsychiatric disturbances in late-life is perhaps a worthwhile contemplation.

4. Summary

In addition to cognitive symptoms, a significant portion of AD patients suffer from depression. Depression has been demonstrated to be a risk factor for AD and suggested to be a possible prodrome for AD. Several common neurodegenerative mechanisms underlie the development of AD and depression, including inflammatory processes, reduced neurotrophic factors, and altered neuronal plasticity. The shared neuropathological processes provide substantial evidence to support intimate relationship between AD and depression. The possibility that depression may lead to neurological disorders does not confine to AD, but could extend to other dementias, PD, and stroke.

Thus far, there is no definitive evidence to associate depression with AD, and the underlying mechanisms regarding the links between depression and neurodegenerative diseases have not been elucidated. Owing to the highly prevalent and devastating natures of these disorders, future research is warranted in order to provide further insights toward the possible existence of pathophysiological associations between these neuropsychiatric conditions; Figs. 1 and 2 summarize the putative associations between depression and AD based on current evidence.

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