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PARALLELS BETWEEN MAJOR DEPRESSIVE DISORDER AND ALZHEIMER'S DISEASE: ROLE OF OXIDATIVE STRESS AND GENETIC VULNERABILITY

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Abstract

The thesis of this review is that oxidative stress is the central factor in major depressive disorder (MDD) and Alzheimer's disease (AD). The major elements involved are inflammatory cytokines, the hypothalamic pituitary axis, the hypothalamic pituitary gonadal, and arginine vasopressin systems, which induce glucocorticoid and "oxidopamatergic" cascades when triggered by psychosocial stress, severe life threatening events, and mental-affective and somatic diseases. In individuals with a genomic vulnerability to depression these cascades may result in chronic depression-anxiety-stress spectra, resulting in MDD and other known depressive syndromes. In contrast, in subjects with genomic vulnerability to Alzheimer's disease, oxidative stress-induced brain damage triggers specific antioxidant defenses, i.e. increased levels of amyloid-β (Aβ) and aggregation of hyper-phosphorylated tau, resulting in paired helical filaments and impaired functions related to the ApoEε4 isoform, leading to complex pathological cascades culminating in AD. Surprisingly, all the AD associated molecular pathways mentioned in this review have been shown to be similar or analogous to those found in depression, including structural damage, i.e. hippocampal and frontal cortex atrophy. Other interacting molecular signals, i.e. GSK-3β, convergent survival factors (brain-derived neurotrophic factor and heat shock proteins), and transition-redox metals are also mentioned to emphasize the vast array of intermediates that could interact via comparable mechanisms in both MDD and AD.

Keywords

Alzheimer's disease; amyloid β; lipid peroxidation; major depressive disorder; nucleic acid oxidation; oxidative stress; tau

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

1. INTRODUCTION

Depression, one of the most widely disseminated neuropsychiatric diseases in the world, has been recognized for centuries and has been treated by many different methods throughout history. Although numerous studies of depression have been performed through the psychological-environmental, social-ethnical-statistical, and biological-neuroscience fields, its etiology, diagnosis, pathogenic mechanisms and treatments are still far from being completely elucidated (Gruenberg et al. 2005). Reviewing the evolution of the two main diagnostic tools currently in use – Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) – we observe a series of changes and revisions, particularly in the field of mood disorders. Since 1952, when DSM-I was published, it has undergone significant revision every 5 to 10 years due to the uncertain knowledge of the neurobiological processes underlying the observed symptoms of depression (Parker 2000). Even with the help of sophisticated studies taking decades to complete, and with the support of international diagnostic categorizations of mental illnesses, depressive syndromes still cannot be clearly codified and understood because these classifications are observational and lack underlying pathogenic cellular and molecular neurobiological and pharmacologic-etiologic mechanisms and phenotypes (Gruenberg et al. 2005; Starkstein et al. 2005; Akiskal and Lewis 2005; Brown et al. 1994; Parker 2000). Nevertheless, in our opinion, one of the most useful approaches to depression, which includes neurobiological, cellular, and molecular studies, is reported by Akiskal and McKinney (1973). These authors consider depression as comprising a spectrum that deviates from normal, and which is split into minor “neurotic” personality-based depression and “endogenous” biologically-based major depression, which is more serious and resistant to treatment. Based on epidemiological and clinical observations, they show that this novel spectrum may be seen as a psychobiological paradigmatic approach, extending from dysthymia, a light acute or chronic syndrome which presents the main depressive traits but which does not usually impair the patient’s activities, ascending to “sub-threshold depressive syndromes”, a complex set of moderate to serious symptoms that wax and wane over time; and at the end of the continuum; severe major depressive disorders (MDD). Although not fully accepted by many clinicians, this psychobiological continuum is consistent with clinical observation, and has been indirectly assessed by neurobiological investigations of depression, leading progressively toward a unified hypothesis (Akiskal and McKinney 1973) that affords much more consistent biologic data. Hence, our review on depression shall incorporate it.

Following the same strategy as that used for depression, we shall consider Alzheimer’s disease and other dementias as a psychobiological continuum, beginning with aging phenotypes and adding variant phenotypes, particularly cognitive, as the aging cognitive impairment, mild cognitive impairment (MCI), gradually progressing into mild to moderate forms of senile dementia of the Alzheimer type (SDAT) (Rodrigues et al. 2010), and ending with deep to very severe dementia. One of the reasons to use this approach is that the neurobiological and molecular processing mechanisms may be studied more openly, without the restriction of ambiguous clinical phenotypes, threshold measures, observation, and opinion. Furthermore, we reported in a previous study (Rodrigues et al. 2010) that if we

consider a closed system cohort - without member inclusion from birth or exclusion at death - going through the continuum of aging, normal aging cognitive decline, MCI and AD; and if all its participants reach 100 years of age, 83% would be affected by AD or SDAT, and the remaining 17% of this 100 year old community would be either normal (not senile dementia--NSD) or affected by other types of neurological disease. Thus, according to the typical AD prevalence, at 100 years old, SDAT participants would be by far the norm (83%), and NSD plus senile dementia of other types would be the exception (17%); factors that make statistical AD evaluation erratic and confusing as to its real prevalence/incidence in the world (Rodrigues et al. 2010). These impressive statistical results, we believe, may represent a chance to go forward on the aging stress-anxiety-depression and neurodegenerative illnesses continuum looking for ‘a common or analogous or alike molecular, biochemical and biological brain mechanisms on AD and depressive spectra’ (Rodrigues et al. 2010).

Oxidative stress in the brain is a result of accumulated free radical damage throughout life that produces signs of molecular, cellular, and clinical pathological phenotypes when the neural antioxidant defenses of the organism are inadequate to counter the reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are constantly produced in the processes of respiration and energy production (Murray 2003). Oxidative stress has been studied intensively, either by basic scientists studying molecular and neuronal phenotypes or through clinical therapeutic applications by physicians in various domains, including those that investigate environmental insults such as radiation [for review see Mazzulli et al. 2006; Liu and Ames 2006; Moreira et al. 2006]. Thus, oxygen and hydrogen peroxide derived free radicals, nitric oxide (NO) derived peroxynitrite, and many other dependent free radicals form a chain of neurobiological events that may damage DNA, proteins, fatty acids and carbohydrates, leading to formation of 8-hydroxy-2′-deoxyguanosine, carbonyl side groups, 4-hydroxy-nonenal (4-HNE), and advanced glycation end-products (AGEs), respectively (Jellinger 2007). When chronic diseases, aging, trauma, chronic major depressive disorder, to name a few conditions, occur in an organism, free radical antagonists and natural antioxidants may become insufficient to maintain oxidative homeostasis. The molecular defenses, even though continuously expressed, are destined to respond defensively and finally fail. Then, as a consequence of continuous respiration, oxidative stress begins to damage a series of macromolecules either in the cytosol, nucleus, and/or mitochondria. This dynamic damage, occurring throughout the course of life, leads to a series of “cascades” which may end in neuronal death by apoptosis and/or necrosis (Mazzulli et al 2006). Although great progress has been made, too much has yet to be elucidated for us to fully understand the complexity of oxidative stress signaling and how the structural and functional impairment incurred leads to cellular demise. Oxidative stress is one of the main molecular and cellular factors in triggering “cascades” which may interact with the most varied molecular phenotypes, impairing neuronal function and transforming subclinical, physiological, and homeostatic neural defense mechanisms toward disease and neuronal disintegration (Jellinger 2007). Further, it is possible to consider oxidative stress as a dynamic continuum of brain response in the same context as aging, aging cognitive decline, depression, mild cognitive impairment, and Alzheimer’s disease, once the first two physiologic phenotypes proceed and transform into the last three pathologic phenotypes,

depending on internal and external conditions (Rodrigues et al 2010). In this review we will also consider chronic major depressive disorder, in comorbidity with anxiety and/or psychological stress, as a continuous spectrum of subclinical, clinical, and biologic molecular phenotypes (Akiskal and Lewis 2005). In addition, we present studies showing that long term depression may interact with oxidative stress and AD, as well as inflammation, cytokines and other neuroendocrine pathways that were more recently revealed. We will examine their equivalent similarities, interactions, and cross-talk in clinical and biological-molecular signaling. Finally, we will assess whether the clinical, pharmacologic, psychiatric, neurologic, immunologic, endocrine, and genomic studies demonstrate analogous dynamic molecular processes in the development of both brain pathologies and outline the implications for treatment changes suggested by this new analysis. In the first phase of life, youth, metabolism and energetic forces, resulting from oxidative phosphorylation, generate large quantities of free radicals in the brain. Nevertheless, robust antioxidant protection from free radicals usually controls the damage to neurons. During this time stochastic mutations in mitochondrial and nuclear DNA occur; however, the disruption of homeostasis, oxidation of protein, fatty acids, sugar, and DNA that would lead to neural apoptosis is efficiently counteracted, allowing normal aging without brain pathology. Toward middle age, accumulated damage from oxidative stress may put the brain at risk. This second phase ("metabolic and energetic oxidative stress cascade"), resulting from long-term generation of free radicals during aging, induces stronger neurobiological oxidation cascades and leads to greater free radical production, more mitochondrial, nuclear DNA and protein lesions. Stochastic errors occurring in transcription and translation along with mutations in DNA throughout the adult years may lead to neurodegenerative processes if not countered by the now declining antioxidant systems. In a third phase, which could be labeled as "senescence oxidative stress – amyloid β (Aβ) aging cascades", the oxidative damage and Aβ cascades may be initiated as a result of now over-extended antioxidant aging defenses. Thus, the interaction of continuous and long term nuclear and mitochondrial DNA damage in conjunction with the increased defensive deposition of Aβ and hyper-phosphorylated tau particularly, may result in neurodegenerative phenotypes as neurons and glia die; and as senility of the Alzheimer type intensifies (Rodrigues et al 2010; Figures 1–4) Finally, we have emphasized that aging, "time in which all metabolic, genetic, protein and macromolecular dynamic interactions maintain homeostasis but decline as a result of impaired ability to maintain balance", is considered the main risk for oxidative stress because it is over time that oxidation processes normally take place, whereas all negative intrinsic and extrinsic factors constantly act against the brain and other organ systems. Oxidative damage, originating from free radicals, accumulates silently in all life stages and in many brain regions, with no significant symptoms or signs, and more intensely in elderly individuals. We have, in previous work, emphasized that in view of the interaction of many processes and signaling pathways involving large numbers of macromolecules and production of enzyme/protein during life, it is not surprising that a significant number of genetic, transcription, and translation errors and biases during this continuing dynamic living process may contribute to oxidizing, damaging, and ultimately killing neurons and glia, resulting in pathogenesis in the brain, neurodegenerative illness being the most characteristic example ((Rodrigues et al 2010;

Murray 2003; Mazzulli et al. 2006; Liu and Ames 2006; Moreira et al. 2006; Jellinger 2007; Littlejohn et al. 2010).

As a first step, we describe the relationship of depression and Alzheimer's disease in clinical fields, where many studies are currently underway and for the last 20 years. A number of clinical studies - including robust investigations with over 1000 subjects - show that mood disorders are a moderate to high risk factor for AD (Devenand et al. 1996; Kessing and Nilsson 2003) and that 30% – 50% of depressive patients develop MCI and AD. This result suggests models for AD and MDD that are consistent with clinical and statistical reports (Green et al. 2003). As a second step - that sets up the main and major part of this review - the endocrine, immunologic, psycho-neural-pharmacological, neurochemical, neurobiological and molecular phenotypes will be assessed, particularly those that support the common factors in either MDD or AD pathology. We present putative interface models between chronic major depressive disorder/anxiety/stress and Alzheimer's disease and their links with oxidative and nitrosative stress as a primary initiation event in pathogenesis. Finally, we discuss some common psycho-neural-pharmacological therapies based on this review that may be effective for both neural-psychiatric syndromes.

2. CLINICAL ASPECTS

For more than five decades a variety of reports and studies have shown a robust clinical association between AD and chronic MDD, with or without anxiety, and particularly behavioral and social stress. One of the most important points of these studies is the need to recognize the advent of AD in depressive patients, as their clinical condition is more serious than that of MDD-free patients (Littlejohn et al. 2010; Devenand et al. 1996; Kessing and Nilsson 2003; Green et al. 2003). A report by Green et al. (2003) directly addressed these concerns. In the Alzheimer's Genetic Epidemiology (MIRAGE) Study the authors selected 4,046 individuals from 1,953 families. From this sample 1,778 subjects were diagnosed with probable AD and 175, examined post mortem, had a confirmed diagnosis of AD. The remaining 2,093 non-demented family members were questioned about depressive symptoms and other AD risk factors. The data revealed a significant association between depressive symptoms and AD: the odds ratio (OR) of this relation for all persons examined was 2.13 (C.I. 95%). The important conclusion was that in families with an AD member where depressive symptoms occurred one year before the onset of dementia, the association of those illnesses had an OR = 4.57 (C.I. 95%). Depressive symptoms occurring either more than one year before (OR 1.38, C.I. 95%) or over 25 years before (OR 1.71, C.I. 95%) the onset of dementia still showed a significant association with AD. The conclusion was that there is a strong association between depressive symptoms and Alzheimer's disease, even when the depression occurred over 25 years before the appearance of clinical AD. These findings are consistent with other articles, i.e. the study of Alexopoulus and colleagues (2003), who reported that "pseudo-dementia" or reversible dementia – a syndrome with a cognitive clinical phenotype, but actually expressing a major depressive episode (Caine 1981) - manifested by 23 patients with geriatric depression, were 4.7 times more likely to develop permanent dementia than 37 depressive elderly patients without cognitive impairment, in a 33.8 month follow-up. A study of clinical risk factors obtained performed with medical records on a population-based case-control study over 14 years from the Mayo

Clinic, Rochester, MN (Author-Kokmen et al. 1991) reported that among more than 20 risk factors for AD, the most statistically significant was episodic depression. Only two other risk factors were identified: hypertension and personality disturbances. In a brief communication Pomara and Sidtis reported that the 28% reduced cortical thickness in parietal and temporal regions of the brain observed in relatives (children and grandchildren) with major recurrent familial depression disorder was comparable to the cortical thinning they observed in some neuropsychiatric disorders, including Alzheimer's disease. These cortical AD like changes were considered to be predictors of dementia, even in asymptomatic amyloid positive older controls (Pomara and Sidtis 2009) Many studies evaluating regional cerebral glucose metabolism through positron emission tomography (PET) in subjects with chronic depression have been published over the past two decades (Geerlings et al. 2008); some of the results showed widespread reduction in the regional cerebral metabolic rate for glucose, compared with normal non-depressive and matched controls. The study by Kumar et al (1993) used 2-[18F]fluoro-2-deoxy-D-glucose PET in three groups of eight subjects each: 1-healthy age-matched controls; 2-late-life depression; and 3-probable dementia of the Alzheimer type. They found that Groups 2 and 3 had more significant reduction of glucose metabolism in most of the major cerebral neocortical, subcortical and para-limbic regions than did Group 1. The decline in glucose metabolism in Groups 2 and 3 did not differ significantly. Furthermore, glucose hypo-metabolism was the same in dementia of the Alzheimer type or late-life depression, although the subjects with depression demonstrated a more homogeneous pattern of metabolic processing and no preferential involvement of any region. The authors concluded that a larger sample size should be used to study the similarity in the pathogenesis of depression and dementia of the Alzheimer type. In another large study conducted at two traditional Institutions in Amsterdam, the Amsterdam Study of the Elderly (ASTEL) and Longitudinal Aging Study Amsterdam (LASA) community based, a subgroup of more highly educated elderly, depression seemed to be an early manifestation of Alzheimer's disease before cognitive symptoms become apparent (Geerlings et al. 2000; Zaudig 2005). A possible conclusion from the ASTEL or LASA study samples is that the dementia process may be preceded by depression/anxiety and stress. Many studies of genetic vulnerability to depression show an inability by the individual to withstand excessively severe demands of life that results in chronic depressive and stressful living. In many patients presenting with MCI or AD, clinicians report histories of serious losses in life, such as estranged family members, economic failure, difficulties in social relations, isolation, and alcohol dependence, among others (Kessing and Nilsson 2003; Alexopoulos et al. 1993; Zaudig 2005). Furthermore, other studies investigating the relationship of depression and AD, stratified by the reason depression onset/year, observed an odd ratio of 2.0 (95% CI = 0.9–4.6) for depression that occurred more than 10 years before the onset of dementia symptoms, and an odd ratio of 0.9 (95% CI = 0.2–3.0) for depression onset less than 10 years before the onset of dementia symptoms. The conclusion of this study was that depressive episodes occurring well before onset of dementia symptoms appear to significantly increase the risk of Alzheimer's disease (Brown et al. 1994; Moreira et al. 2006; Jellinger 2007; Littlejohn et al. 2010). Nevertheless, these findings, which are consistent with many other reports (Geerlings et al. 2008), reveal that a detailed history of depression is critical and was the only independent factor found in this group of AD patients. In this view, geriatric depression with reversible dementia

(Alexopoulos et al. 1993) is a coherent phenotype that illustrates high brain cortisol involvement: cognitive impairment in these generally acute depressive patients may subside with resolution of stress-depression. Commonly referred as “pseudo-dementia” (Caine 1981), this transitory syndrome may occur in late onset depression; if the cognitive impairment remains in spite of improvement of the affective disorder, the risk for neurodegenerative illness increases to 40% in about three years (Shanmugham and Alexopoulos 2005). As discussed below, both hippocampal damage and the consequent memory impairment produced by the “cortisol cascade” in acute depression are reversible; but a chronic “cortisol cascade” leads to hippocampal and cortical atrophy.

Additional clinical studies have been performed, including systematic reviews and complete meta-analyses of the relationship between depression and AD; for example the report of Ownby RL et al (2006) concluded - after a pooled and meta-regression analyses of 20 selected studies aggregating 102,172 persons in 8 countries and through on-line assessment – that depression, in spite of being a high risk for AD, may be a prodromal symptom. Wilson et al (2002) reported that vascular disease was an independent risk factor from the data obtained on the relationship of depression and MCI; but, for high depressive patients with vascular brain impairment, it was found that about 20% presented with cognitive impairment. Finally, further studies consider it important to distinguish objectively between depression and dementia in older persons, which may alert physicians to the strong cognitive and mood symptom correlates, giving noteworthy prominence to integrated treatments of both dementia and depression, which may be preferable to treating them independently (Wright and Persad 2007).

3. NEUROENDOCRINE-DEPENDENT OXIDATIVE STRESS AND HIPPOCAMPAL ATROPHY: A BRIDGE BETWEEN ALZHEIMER’S DISEASE AND MAJOR DEPRESSIVE DISORDER?

In the 1930s the discovery of adrenal cortical steroids, particularly cortisol, gave rise to a period of euphoria in medical communities all over the world over the potential therapeutic applications. Since it was shown that the adrenal gland hyper-secretes cortisol in a number of major depression disorder patients (melancholia), this hormone has played an essential role in psychiatry and extensive research is currently ongoing. In the 1940s many psychiatric disorders were treated with either extract from adrenal cortex or cortisol with positive results. Furthermore, the endocrine, psychiatric, and neurologic fields presented so many interactions that psycho-neuroendocrinology and endocrine psychiatry became specialized fields in either research or clinical neuropsychiatry (Shorter and Fink 2010).

Current neuroscience and neurochemistry establish that the stress (in this context psychological stress) response by the brain is mediated through the hypothalamic-pituitary-adrenal axis, most likely, though not firmly established, by stimuli brought from the amygdalae nuclei and other neural systems (Arborelius et al. 1999). So, in the hypothalamic paraventricular nucleus there is higher synthesis of corticotrophin releasing factor, which is discharged to the local portal-vascular system by the median eminence neurons, reaching the anterior pituitary gland. In this structure, after stimulation of corticotrophin releasing factor

receptors, adrenocorticotrophic hormone (ACTH) and other derivatives of pro-opiomelanocortin are synthesized in a cascade-like process (Plotsky 1991). ACTH, in turn, elicits the synthesis of glucocorticoids (cortisol and corticosterone, in humans and primates respectively) from the adrenal cortex. In the limbic system, particularly the hippocampus, septo-hippocampal nucleus, and amygdala, the adrenal hormone binds to mineralocorticoid receptors and to glucocorticoid receptors. During stress, cortisol levels rise about 100-fold and the glucocorticoid receptors stimulate the hypothalamic paraventricular nucleus and the hippocampus (Jacobus and Sapolski 1991). The main function of the mineralocorticoid receptors and glucocorticoid receptors is to suppress stress-induced hyperactivity of the hypothalamic-pituitary-adrenal axis, leading to the inference that the modulator function of this hormonal system is dependent on glucocorticoid feedback mechanisms to inhibit its stress-triggered activation, and to critically diminish additional glucocorticoid secretion. Furthermore, the medial pre-frontal cortex also contributes to hypothalamic-pituitary-adrenal axis stress modulation, i.e. inhibition: this frontal brain region converges with the hippocampal formation onto certain regions of the anterior bed nucleus of stria terminalis and both project GABAergic fibers to the paraventricular nucleus of the hypothalamus, demonstrating that the hypothalamic-pituitary-adrenal -inhibitory influences of medial prefrontal cortex and hippocampal formation are exerted principally through a convergence to a common relay (not parallel or serial), which produces a strong modulatory mechanism (Radley and Sawchenko 2011). An important and consistent finding reported over 20 years ago is the significance of testing MDD by administration of dexamethasone and corticotrophin releasing factor, unveiling a very sensitive measure to this illness - the real meaning of this finding was not appreciated at that time when psychoanalysis was the main tool for understanding depression. Nonetheless, today the dexamethasone-corticotrophin releasing factor test – a double and reinforced test -- has demonstrated that there is likely a threshold to abnormalities of hypothalamic pituitary adrenal axis function in depressed patients, which may implicate a genetic vulnerability to MDD (Holsboer et al. 1995). Genetic predisposition is only a partial explanation since a significant proportion of patients without depressive/anxiety/stress may develop Alzheimer’s disease; and a significant fraction (approximately 60%) of chronic major depressive and/or anxious-stress patients do not develop AD. A number of studies have focused on the genotypes of depressive patients using single nucleotide polymorphisms, either in MDD or AD. As an example, the short mutant alleles of the serotonin transporter (5-HTT) gene (Canli et al. 2003; Caspi et al. 2003) and the corticotrophin-releasing hormone receptor-1 gene associations with MDD (Liu et al. 2006) may explain why approximately 40% of depressive patients show resistance to antidepressants and to psychotherapy. Furthermore, in Alzheimer’s disease, there is an extremely complex set of genetic factors that result in a 30% increase of AD in families, compared to controls; this includes all forms of early onset AD and late onset AD. These genetic puzzles underscore the uncertainty and need for additional research to understand the genotypic vulnerability in both pathologies and to determine what level the environmental and socio-ethnical factors influence the diseases’ expression (Coppedé and Migliore 2007; Haines et al. 2000). Thus, the hypothalamic pituitary adrenal axis is currently considered to be the ‘final common pathway’ for a major part of the depressive and stress-anxiety symptomatology. Furthermore, most of the environmental and gene dependent phenotypes appear to associate positively with the corticotrophin-releasing

hormone-ACTH-Cortisol axis activity in depression, and antidepressants may return these hormones to normal levels (Bao et al. 2008). The majority of pertinent investigations, including those related to other hypothalamic hormones, e.g. oxytocin (Meynen et al. 2007), have firmly established this point.

The assumption that chronic depression-stress syndromes elevate glucocorticoids persistently, the “glucocorticoid cascade hypothesis” (Sopolsky et al. 1986) in the hippocampus and medial frontal cortex particularly, raises the question of what the action of these hormones is on these regions. The pioneering studies of McEwen and Magarinos (2001) have shown that the hippocampus, which is involved in declarative, spatial and contextual memory, is very sensitive to stress and gonadal hormones. According to these authors the hippocampus is a very plastic structure exhibiting four main effects from adrenal steroids and estrogens: 1 - the effect of estrogens; 2 - synapse formation in physiological levels (Woolley et al. 1990) with participation of excitatory amino-acids and inhibitory (GABAergic) interneurons (Gazzaley et al. 1996; Gould et al. 1998; Eriksson et al. 1998); and adrenal steroids: 3 - granule neuron death and apoptosis in bilateral adrenalectomy; and 4 - the blocking of dentate-gyrus neuronal loss by aldosterone (Woolley et al. 1997). This set of observations suggests that neurogenesis/turnover in the hippocampal dentate-gyrus granule cells is controlled by adrenal steroids along with n-methyl-dextro-aspartate (NMDA) receptors and participation of other excitatory amino-acids. As adrenal steroids increase with stress-depression, stress-depression symptoms, mediated by corticotrophin-releasing hormone, may alter neurogenesis, a common and general phenotype in mammals (Woolley et al. 1998), especially – but not exclusively – in the dentate-gyrus (Gould et al. 1998) of the hippocampus, inducing neuronal apoptosis and death, hippocampal atrophy, and memory deficits (Lupien et al. 1990). Furthermore, after these and many other relevant studies over the last two decades (Lupien et al. 1994; Lupien et al. 1995; Lupien and McEwen 1997; Scolville and Milner 1957; Porter and Landsfield 1998; Sapolsky 2001; Czéh et al. 2001), hippocampal atrophy has been quantitatively associated and positively correlated with glucocorticoid levels in various neuronal regions of this structure, either in animal stress models or in humans, particularly in depressed elderly animals or patients. Two other relevant findings show that increased glucocorticoid hormone levels may be associated with the decline in volume, decreased level of essential metabolites, and attenuated neurogenesis in the stress-induced hippocampal structure, compared with non-stressed, matched controls. This damage is prevented by the use of antidepressant treatments (Czéh et al. 2001; Ballmaier et al. 2008), particularly in aged subjects with long-term depression (Landfield and Linch 1978; Issa et al. 1990).

Moving to Alzheimer’s disease, there are relevant studies from the 1980s and 1990s: Davis et al. (1986) reported that cortisol levels are elevated in Alzheimer’s disease compared to controls. The 24 hour mean and integral plasma cortisol concentration is elevated significantly compared to controls in Alzheimer and Parkinson diseases (Hartmann et al. 1997). Furthermore, increased cortisol levels in AD are correlated with hippocampal atrophy (de Leon et al. 1997); and the cortisol response to the opioid antagonist naltrexone was absent in AD in individuals of comparable age to healthy controls who show elevated cortisol levels in this situation. This suggests that neuroendocrine abnormalities might be an important concomitant and possibly a central contributor to the pathophysiology of

Alzheimer's disease (Pomara et al. 1988). In a study of cortisol levels in the cerebral spinal fluid (CSF) of elderly patients with depression and AD, compared with not-depressive-AD and healthy elderly controls, Hoogendijk et al (2006) reported some paradoxical results: the CSF cortisol of depressed-AD subjects had a greater than twofold increase in the CSF cortisol compared to controls and did not differ from the not-depressed-AD CSF cortisol levels, apparently indicating that depression does not contribute to the cortisol CSF levels. They concluded that if depression-AD has about the same brain cortisol levels as AD, and both pathologies associate with double the level of cortisol compared to healthy controls, different neurobiology and molecular mechanisms occur in AD and MDD. We could dispute these results since, while cortisol levels can double as depression develops and progresses to depression-AD, the data on advanced AD patients may represent cortisol levels without any contribution from depression. Since there are no depressed-only individuals in this group, it is not possible to assess the contribution of depression alone to cortisol levels and to compare these findings with AD, depressed-AD and control subjects. Demonstration that AD and MDD employ different biological mechanisms requires determination of whether depression causes the same results as patients with depression-AD, and to characterize the underlying mechanisms under both circumstances. In any event, this interesting study shows the critical importance of AD on cortisol levels or the inverse – cortisol levels on AD – and suggests, consistent with our proposal, that additional investigation into this issue is needed.

4. PSYCHOSOCIAL STRESS-ANXIETY-DEPRESSION and OXIDATIVE STRESS

The generation of ROS and RNS is a physiological and normal attribute of almost any aerobic event of organismic animal life. The "oxygen paradox" was established in the middle of the 20th Century. It establishes that: "O_2, the most important substrate of life, may be also the most relevant factor of death" since, aerobic organisms decline in their defenses against its toxicity throughout life. In spite of the fact that 95% of O_2 is metabolized to water, about 5% of it, under normal conditions involving complex pathways, may produce ROS and RNS; particularly in the brain, which is the most vulnerable organ to oxidative damage, by reason of its peculiar physiologic and structural characteristics (Jellinger 2007). In spite of relevant physiological responses, pathophysiological conditions induced by free radicals may cause DNA damage, protein oxidation, and lipid peroxidation, resulting in tissue lesions, particularly in cell membranes (Toro and Rodrigo 2009; Behl et al. 1997). Conversely, the hippocampus may suffer damage from stress-depression-anxiety, particularly in chronic conditions; and the stress hormones, particularly the glucocorticoids, mediate this "cross-talk" between depression and hippocampal lesions (Bremner 1999) through disruption of cellular metabolism (Sapolsky et al. 1990; Sapolski 2000) and altering synaptic structures in specific areas such as CA1 (Magarinos et al. 1997). Moreover, single positron emission computerized tomography (Mayberg et al. 1994) and magnetic resonance imaging (Ballmaier et al. 2008), in addition to other neuroimaging investigations, have shown that depressed patients have significant differences in functional and structural parameters, particularly in the para-limbic, temporo-frontal, and hippocampal brain regions, compared with controls matched for age, sex, cultural, and ethnic characteristics. On the other hand, glucocorticoids have been shown to enhance levels of cell damage in chronic

stress-depression-anxiety syndromes and, as such, to elevate the oxidative stress load causing molecular dysfunction and neuron death (Behl et al. 1997). Mineralocorticoid receptors and glucocorticoid receptors, a dual glucocorticoid-binding receptor system, influence the hypothalamic pituitary adrenal axis, inhibiting oxidative stress damage to limbic structures, particularly hippocampal regions, acting as negative feedback and tonic inhibitory influences (De Kloet and Reul 1987; De Kloet et al. 1998) at the hypothalamic and pituitary level and at the pyramidal (CA1–4) and granular (dentate gyrus) neurons of the hippocampus (Herman et al. 1989; Herman and Cullinan 1997). Interestingly, there are also strong molecular and cellular influences on serotonergic transmission, neuronal excitability, and behavioral responses in addition to hypothalamic pituitary adrenal regulation, effects that are relevant and consistent with our suggestions (De Kloet et al. 1998; Bitran et al. 1998).

THE MOLECULAR MECHANISM OF HIPPOCAMPAL ATROPHY

Glutamate is the most abundant excitatory amino acid in the brain, where it is normally released by an estimated 40% of all synapses (Fonum 1984; Chalmers et al. 1990). As we will discuss below, the “glutamatergic” hypothesis of AD postulates that elevated glutamate levels in the hippocampus, frontal-temporal cortex, and other brain regions leads to activation of glutamate receptors on the neuronal, glial, and mitochondrial membranes, particularly NMDARs, opening the channels to calcium (Ca2+) entry into the synapses and through diffusion to intracellular domains. Glutamate kills neurons by two main mechanisms: through pathways mediated by NMDARs, and via the “oxidative pathway” which includes Ca2+ as an inducer of oxidative stress. As many antioxidants can block the damage from either biochemical process, the production of reactive oxygen and reactive nitrogen leading to oxidative stress is the most probable cause and is consistent with the glutamatergic killing of neurons. Furthermore, catechol-amines, particularly dopamine, may act in concert with glutamate in a complex biochemical process favoring neuronal damage through oxidation pathways (Mahler and Davis 1996). The continuous release of dopamine at normal or excessive levels may induce excitotoxic concentrations of glutamate to stimulate a series of oxidative signaling pathways, which may end in neuronal and/or glial death. Most of these pathways are not clear, although some have been already characterized. A major source of free radicals is hydrogen peroxide (H_2O_2), which is continuously generated within cells as a result of the organism’$_s$ respiration. If not countered, H_2O_2 can accumulate to lethal levels and may jeopardize neuronal survival (Halliwell and Gutteridge 1993). Glutathione peroxidase (G-Px) is the critical enzyme in preventing free radical OH formation from H_2O_2 through the Fenton reaction with the redox transition metal Fe+++/Fe ++. The interesting study of de Haan et al (2007) about the “gene dosage effect” in Down’s Syndrome (DS) shows that it is the ratio of superoxide-dismutase 1/G-Px - the first enzyme converting superoxide radicals O_2^- to H_2O_2, and the other inhibiting hydroxyl radical formation – that constitutes the critical defense against metabolism-dependent oxidative stress in neurons. Furthermore, the interaction of dopamine with glutamate (Mahler and Davis 1996) inhibits cysteine transport into neurons (Murphy et al. 1989; Oka et al. 1993; Davis and Mahler 1994) which gives rise to an inability to maintain intracellular glutathione levels – the substrate for G-Px defenses. Thus, the low catalase concentration in neurons in combination with the reduced levels of intracellular glutathione lead to a reduced ability to

synthesize G-Px and protect against oxidative reactions within the cell and, ultimately, to cell death (Greene and Greenamyre 1995; Gwag et al. 1995). In previous sections it was shown that hippocampal atrophy is associated with chronic stress and major depressive disorders in more than 55% of affected individuals (Sheline et al. 1996) and, that MK-801, an N-methyl-D-aspartate (NMDA) antagonist, attenuates dendritic hippocampal loss and other damage incited by stimulation of NMDARs (Nitsch and Frotscher 1992). As shown in this study, recurrent major depression and chronic psychosocial stress are associated with hippocampal atrophy. However, dendritic hippocampal loss and posttraumatic reduction of the "early gene" activation by the NMDAR antagonist MK-801 demonstrates that NMDAR stress stimulation causes atrophy in some hippocampal areas; and chronic stress, provoking excessive liberation of CRH in hypothalamus and hippocampus, initiates the "corticoid cascade" hampering homeostasis in the HPA which stimulates neurotransmitters, including monoamines and neuropeptides, as a consequence of the robust increase in glucocorticoid levels. Since the 1990s, glutamate has been studied as a neurotoxic agent (Fonum 1984) and oxidative stress and neurodegenerative diseases have been hypothesized as originating as a result of the continuous over-stimulation of some brain regions, particularly the hippocampus, limbic system, and mesial fronto-temporal neo-cortex. The "glutamatergic" hypothesis of AD establishes that elevated activation of the glutamate receptors in the neuronal, glial, and mitochondrial membranes, particularly NMDARs, opens calcium channels allowing Ca^{2+} entry into the synapses and diffusion throughout the cytosol, near plasma and mitochondrial membranes of the post-synaptic cells (Coyle and Puttfarcken 1993). Excessive Ca^{2+}, inducing a series of downstream signaling and molecular pathways, facilitates excitotoxicity or neuronal apoptosis/necrosis and consequent cellular death through glutamate/Ca^{2+} dependent molecular mechanisms (Del Rio and Frenchilla 2006; Sapolski 2000). Before describing the current studies on oxidative stress, corticoid elevation, depression, hippocampal atrophy, and cytokines as a lethal triggering of the "glucocorticoid cascade", it is important to mention the roles of dopamine, particularly on oxidative stress, and its interactions with behavioral psychosocial stress and depression. Indeed, dopamine is the major catecholaminergic neurotransmitter in the brain and dopaminergic neurons. Dopaminergic neurons are located in the substantia nigra, constituting some of the dopaminergic pathways responsible for loco-motor movement, motivation and reward, and secretion of pituitary gland hormones. Dysfunction of these systems can lead to a series of neurological, psychological, and endocrine diseases, Parkinson's disease (PD) being one of the best examples (Vallone, Picetti, Borelli 2000). Currently there is increasing evidence that dopamine, besides acting as a neurotransmitter, can become neurotoxic at high concentrations or, in an oxidative environment, at normal levels. The evidence has been derived from idiopathic PD, even though the substantia nigra is not the only region in the brain affected by dopamine oxidative toxicity. The major pathological hallmark is the progressive degeneration of the neuro-melanin-containing dopaminergic neurons in the substantia nigra *pars compacta*, demonstrated in increased post-mortem iron content (Bindoli, Rigobello, Deeble 1992), causing the symptoms of tremor, rigidity, and bradykinesia. The interplay between high dopamine content and free radicals is believed to promote oxidative stress in the case of gene-dependent vulnerability frail defenses, killing neurons in the substantia nigra, mesocortical, and/or mesolimbic systems (Gille and Riederer 1995). Excess dopamine may also be a potent pro-oxidant or a neurotoxic agent via non-

oxidative pathways (Luo et al. 1999; Hattori et al. 1998), and its enzymatic or non-enzymatic oxidation yields redox-active free radicals and the robust pro-oxidant dopamine-quinones and semiquinones which may generate tetra-hydroisoquinones that generate even more dopamine-induced oxidative stress (Vallone, Picetti, Borelli 2000). Finally, dopamine may be oxidized Weingarten, Bermak, Zhou 2001; Pedrosa and Soares-da-Silva 2002), boosting its neuronal killing potential, provoking univalent reduction of oxygen and consequent production of superoxide anion, hydrogen peroxide, and hydroxyl radical (Bindoli, Rigobello, Deeble 1992). Moreover, as the non-catalyzed, physiological oxidation of dopamine is slow, free-transition metal ions like iron and manganese may accelerate its oxidation via biochemical processing mentioned above (Lloyd 1995; Jimenez et al. 1993), closing a cycle that we may label as an “oxi-dopamatergic cascade” (oxidation-glutamate-dopamine oxidative stress).

Meanwhile, despite the attraction of the “corticoid cascade” induced by glutamate-dopamine-oxidative stress, either in chronic psychosocial depression- stress or in associated MCI/AD neurodegenerative damage, we feel that the glutamatergic neurodegenerative hypothesis (Engelhardt, Laks, Cavalcanti 2003) does not explain neuronal and glial death in AD and other neurodegenerative diseases. In these reports, oxidative stress is only superficially mentioned and considered a secondary factor. There are no reports on the concomitant dopaminergic robust influences and interactions with the oxidative stress-induced glutamate cytotoxicity (Avshalumov and Rice 2003; Chen et al. 2011) and the influence of transition redox metals (Calabrese et al. 2007; Perry et al. 2002; Huang et al. 1999; Nunomura et al. 2001; Jennings et al 2006). Additionally, previous studies (Chalmers et al.) showed that glutamatergic receptor binding sites have differential performances in signaling pathways: although NMDA receptors were reduced 40% in the frontal cortex in SDAT, indicating a general NMDAR loss in the presynaptic terminals, kainate receptor binding was increased approximately 70% in deep layers of SDAT frontal cortex, and quisqualate receptors were unaltered. These differences in glutamate receptor actions and structures may indicate that the glutamatergic hypothesis of neurodegenerative diseases is inadequate for explaining all the neurochemical pathways and phenotypes. In our opinion, considered altogether, it would be better to amend the “glutamatergic hypothesis” to one that includes glutamate-dopamine-oxidative stress-induced neuronal, glial death, and synaptic losses. This could be denoted as either a “dopamatergic” or “oxi-dopamatergic” hypothesis of neurodegenerative disorders. However, a question arises from the depression-induced glutamatergic hypothesis: as Ca^{2++} intracellular influx is dispersive and would not kill 20% of the hippocampal/cortical neurons by oxidative stress, the “oxi-dopamatergic” hypothesis could in part explain the large increase of neural and glial oxidative stress killing. The initial glutamate induced ROS and RNS formation may mediate the neurotoxicity of dopamine (Sprague, Everman, Nichols 1998; Kuhn and Geddes 2000; Gudelsky and Yamamoto 2003). The consequent reduction in indoleamine and catecholamine turnover on the synapses, intra, and extra cellular realms is not clear, but may induce initial massive increased serotonergic levels and posterior long-term 5-HT decline; and to severe dopamine imbalance (Baumann and Rothman 2008). Our proposal then, suggests that in addition to the direct “oxi-dopamatergic” oxidative stress, the “corticoid cascade” induction to hippocampal atrophy is,

on the other hand, reinforced by indoleamine/catecholamine neuronal imbalances, which may complete the cycle in MDDs.

5. HOW DO DEPRESSION, THE CORTICOID CASCADE AND OXIDATIVE STRESS INTERACT?

We consider this question to be exceptionally significant and explanatory, since oxidative stress and hippocampal-cortical atrophy are currently considered (Coyle and Puttfarcken 1993; de Leon et al. 1997; Jellinger 2007; de Leon et al. 1989; Lupien et al. 1998) to be associated with Alzheimer's disease. Additionally, other studies are showing strong association with chronic MDDs, with or without co-morbidity, with glucocorticoid stress-anxiety reactions, which may be an integral part of the disease. There are some indirect studies of the association between oxidative stress and depression; the study of Eren et al (2007) demonstrates decreased levels of reduced glutathione (GSH), glutathione peroxidase (GSH-Px) and vitamin C antioxidants in experimentally induced depression in rats. Lipid peroxidation was conversely elevated in the brains of these stress-depressed rats. The confirmation that the oxidative stress phenotypes in these experimental animals resulted from depression was made based on the normalization of LP and GSH-Px after administration of lamotrigine, escitalopram and aripiprazol; medications with recognized anti-depressant effects. Another similar study by Eren et al (2007) showed that the administration of venlafaxine, another classical serotonin with norepinephrine, also a reuptake inhibitor antidepressant, to experimentally depressed rats, reverses the high levels of lipid peroxidation (LP), lowering it to normal levels; and elevates the low levels of cortical GSH-Px, vitamin C and medulla GSH to normal levels. The authors concluded that central nervous system oxidative stress, originating from ROS and RNS stressed neurons and glia, is a phenotype of major depression. These conclusions, confirmed by other studies (Bilici et al 2001; Liu et al. 1996), demonstrate a robust association between major depression and oxidative stress in the central nervous system, and that antidepressant treatments counter oxidative stress, at least in acute episodes. Indeed, reports of hippocampal neuronal damage by oxidative stress as the result of enhanced glucocorticoids were presented more than 15 years ago (Landfield 1994; McIntosh, Hong, Sapolsky 1995; Goodman et al. 1996; Lawrence and Sapolsky 1994), although the reports were mostly isolated and did not show the extensive interaction with other important factors currently envisioned. On the other hand, some deeper studies have been presented on depression, neurodegenerative pathology and the stress system of the human hypothalamus and of the limbic areas and hippocampus. These pioneering researchers emphasize the interaction among all of the above-mentioned factors and report novel data that provides evidence of the influence of the hypothalamic-pituitary-gonadal axis system hormones (gonadotropin releasing hormones –GRHs and andropause menopause hormones) in neurodegenerative diseases of senescence such as Alzheimer's disease (Atwood et al. 2005). They showed that these sex hormones induce a greater number of corticotrophin releasing hormone-expressing neurons in the hypothalamic paraventricular nucleus of men's brain compared to women's brain. This emphasizes their robust involvement not only in senescence, but also in the number of corticotrophin releasing hormone neurons and consequent dissimilar glucocorticoid androsterone and estrogen dependent hypothalamic paraventricular nucleus

concentrations (Bao and Swaab 2007; Bae et al. 2006). On the other hand, glucocorticoids are known to suppress expression in the suprachiasmatic nucleus and paraventricular nucleus of arginine-vasopressin in about 70% of the cells and of corticotrophin releasing hormone in 96% of the cells (Liu et al. 2006; Erkut, Pool, Swaab 1998). In addition to metabolic, immunologic and neuroendocrinologic mechanisms, they influence memory, mood, and behavior (Erkut, Pool, Swaab 1998). Indeed, decay of arginine-vasopressin has an attenuating effect on depression-like behavior; and increased levels of arginine-vasopressin in the paraventricular nucleus induces anhedonia behavior-like depression, despite the lower hypothalamic pituitary adrenal glucocorticoid levels, a paradox suggesting that the vasopressinergic circuits which engender depression-like behavior are separate from those arginine-vasopressin tracks regulating the hypothalamic pituitary adrenal axis (Mlynarik et al. 2007). All these data together are consistent with the findings that oxidative stress, engendered by the “glucocorticoid cascade” in aging, major depression or Alzheimer’s disease (O’Brien et al. 1996; Liu et al. 2000; Mazurek et al. 1986), may induce DNA/RNA damage in the paraventricular nucleus and suprachiasmatic nucleus in the hypothalamus and could suppress arginine-vasopressin gene expression (Liu et al. 2006), decreasing this hormone level −21 the latter suggestion is ours. Accordingly interpreting the accumulated data on the glucocorticoid, vasopressin and sex hormone cascades, it is possible to consider oxidative stress not only as an early direct or indirect factor, but also as an intermediate hypothalamic-pituitary-hormonal factor between AD and MDD. These sex hormone cascades are currently the subject of intensive studies (Roca et al. 2005; Roy, Reid, Van Vugt 1999) and have been shown to be a significant factor in either MDD or AD (Rasmusen et al. 2002). Clearly, oxidative stress is a significant part of the oxidative stress-hypothalamic-pituitary-neural/immune/vasopressin/gonadal/adrenal system with broad influences on either AD or MDD. Finally, the pioneering and central studies of Bao, Meynen, and Swaab (2005; 2011) opened a large track to investigate almost all of the aforementioned interactions and, in spite of some paradoxical data (Swaab et al. 2005), the researchers’ past and recent findings established a clear consensus that is consistent with our proposal.

6. CYTOKINES AND CHEMOKINES: NEUROMOLECULAR SIGNALING IN ALZHEIMER’S DISEASE AND MAJOR DEPRESSIVE DISORDER

Current studies on neuroimmunologic processes in depressive syndromes and AD have suggested new therapeutic strategies for treating these illnesses (Raison et al. 2005). Khan and Alkon (2006) reported that AD involves an induction of signaling pathways, including some brain pro-inflammatory cytokines, the most prominent of which are tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) that are associated with cognitive impairment and low levels of protein kinase-C (PKC). Additionally, cytokine signaling and mitogen activated protein kinases (MAPKs), either in MDD or in AD, induce an extremely complex signaling cascade in response to inflammation. The pathways are initiated by phosphorylation of neuronal membrane receptors, which may be activated by stress, heat, UV, cytokines, TNF-α, growth factor receptors and other cell-cell interactions. The initial event is propagated by phosphorylation of downstream extracellular regulation kinases 1 and 2 (ERK1/2), then jun-NH2 kinases 1 and 3 (JNK 1–3), to p38 proteins (p38), and then to

other substrates. This results in effects on neuroplasticity, neurogenesis, the scaffold structure, core neuronal dynamics and biochemical actions, leading to neuropathological lesions, including neurodegenerative diseases such as AD (Krauss 2001), and stress induced depression, mediated by elevated glucocorticoids and hippocampal atrophy, possibly as a result of oxidative stress. Studies of almost three decades relative to depression/stress/anxiety disorders in a chronic and unexpected progression, have found psycho-immunologic and neurochemical factors associated with emotional behavior and biological phenotypes. In spite of thorough investigations, clear explanations for the neurobiological mechanisms have not yet been reported. Nevertheless, plasma levels of cytokines and chemokines are elevated in depressed individuals, leading to the “cytokine hypothesis” of depression (Snyder 2011). This interesting report, studying a great number of individuals, presented data suggesting an interaction between the antidepressant selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs); and concluded that there is an antagonistic effect between these two agents. The results contradict the common established wisdom (Warner-Schmidt et al. 2011) based on the finding that in plasma, the cytokine levels of IFN-γ and TNFα; and of the small marker protein p11, were increased during depression, decreased by SSRIs treatment, and also lowered by NSAIDs; but in frontal cortical tissues, curiously, the opposite effect was observed. In any case, according to reports from a variety of sources (Calapai et al. 2001; Fiebich, Hollig, Lieb 2001), cytokines, for example, IL-1, IL-6, TNF-α and IFN-γ, do exhibit increased levels in the brain during depression. Furthermore, these cytokines are believed to induce stimulation of corticotrophin-releasing factor, adrenocorticotropic hormone (ACTH), or cortisol in humans; and in this way may be responsible for increased depression/stress/anxiety syndromes and may contribute to the “cortisol cascade”, leading to hippocampal atrophy (McEwen and Magarinos 2001). Therefore, as a recent report shows, one of the roles of the pro-inflammatory cytokines is necessary and sufficient for the anti-neurogenic and behavioral effects of these emotional syndromes. A signaling cascade that may induce the cytokine actions is initiated by NF-kβ, nuclear factor-kβ (Ko Koo et al. 2010). In this study the authors show the association of NF-kβ with inflammation and depression/stress behavioral actions. NF-kβ has a critical role in the IL-1β effects and in stress/depression. Stress inhibits neurogenesis through cortisol action in the hippocampus, leading to hippocampal atrophy (McEwen 1999; Magarinos et al. 1997). Stress and depression are known to be strongly associated with inflammatory reactions, one of the main pathologies in AD brain (Ko Koo et al. 2010; Kaltschmidt et al. 1997). Thus, NF-kβ is a factor in both major depression and AD, its activation in response to inflammatory stimuli decreases proliferation of neural cells. Moreover, chronic depression/stress activates this factor and its downstream signaling, boosting inflammatory responses, suggesting a new therapeutic target for depression. As NF-kβ is a general transcription factor, activated in Alzheimer’s disease, it induces robust stress on hippocampal and other limbic and neocortical neurons by the amyloid-β of senile plaques (SPs) and tau of neurofibrillary tangles (NFTs) (Kaltschmidt et al. 1997). We furthermore emphasize that this transcription factor, which is activated by the cytokine signaling cascade, begins its action in the extracellular tail of the intermembrane cytokine receptors and is transferred to the neural cytoplasm by signaling proteins that constitute the Janus kinases (JAKs), and the transcription factors known as signal transducers and activators of transcription (STATs). Through trans-phosphorylation, these JAK/STAT protein pathways (Gorczynski and Stanley

1999) induce changes in gene expression at the nucleus, binding to DNA promoters. Different cytokines activate the same JAK/STAT signaling pathway, leading to neuronal damage that may constitute a cascade for chronic depression, neurodegeneration and other chronic immune diseases. However, this system is regulated by specific defensive proteins as the suppressors of cytokine signaling and others (Wurster and Grusby 2004).

7. DEPRESSION, INFLAMMATION, OXIDATIVE STRESS AND NEURODEGENERATIVE DISORDERS: DEVELOPMENT OF A RATIONAL "THERAPY" FOR ALZHEIMER'S DISEASE?

The inflammatory and neurodegenerative (IND) hypothesis of depression has its origin in the 1990s, with the cytokine and inflammation associated with oxidative and nitrosative stress-mediated depression research (Sotiropoulos et al. 2011). Neurodegeneration and reduced neurogenesis in chronic depression are directly associated with inflammation, oxidative and nitrosative stress, and mediated in brain cells through immune activation and its long-term consequences (Maes et al. 2011). The study of Catena-Dell'Osso et al (2011) and Myint (2003), following the same rationale stated in the IND hypothesis of depression, establishes that in this illness the cytokines IL-1, IL-6, TNF-α, and interferon-α and γ increase in the brain. Conversely, chronic administration of these cytokines triggers depression, leading to inflammatory oxidative and nitrosative stress, neuronal damage, and to elevation of the enzyme indoleamine-2–3 dioxygenase that catabolizes the AA tryptophan, lowering its concentration and also depleting serotonin in the synapses, an established mechanism for depression. The glucocorticoids are activated, leading to the "glucocorticoid cascade" and dysregulation of the hypothalamic pituitary adrenal axis (Bao, Meynena, Swaab 2008; Sopolsky, Krey, McEwen 1986), reinforcing depression (McEwen and Magarinos 2001). Chronic external stress, and occurrence of anxiety/depression in addition to glucocorticoid elevation in plasma and CSF and the consequent induction of corticoid cascade pathways (Bao, Meynena, Swaab 2008; Meynen et al. 2007; Sopolsky, Krey, McEwen 1986; Woolley et al. 1990) may induce neural-inflammatory responses that induce neurodegeneration and reduced neurogenesis. It was also shown that cytokines (IL-1β, IL-6, IL-12 and TNF-α) increase through induction of depression-mediated hypothalamic pituitary adrenal axis (Thomas et al. 2007). Post-traumatic stress disorders have been reported in some studies to be associated with elevated serum interleukin-6 and IL-6 receptor (IL-6R) concentrations in comparison to controls. When PTSD is a co-morbidity with MDD, IL-6 is higher in serum and is involved in the catecholaminergic modulation of anxiety reactions (Maes et al. 1999). Indeed, there is now evidence that chronic depression syndromes, including anxiety, stress and other autonomic and somatic symptoms such as fatigue, anorexia (hyperphagia), insomnia (hypersomnia), diminished *libido*, apathy, etc., may be the clinical expression of peripheral cell-mediated stimulation, inflammation and induction of inflammatory oxidative and nitrosative stress. If these observations can be linked to the studies on single nucleotide polymorphism of the serotonin transporter (5-HTT) genes (Canli et al. 2005; Caspi et al. 2003) and of the MDD related CHR-receptor-1 gene (Liu et al. 2006), we may state that genetically influenced depression-anxiety phenotypes may already exist beginning at birth and, under severe life stresses, diseases, and/or complex signaling pathways (Dunn 2007), progress to clinical levels.

Moreover, depression often expresses with multiple co-morbidities such as neurodegenerative dementias, stroke, immunological, cardiovascular, obstructive pulmonary diseases, obesity, infections, trauma, interferon-α-based immunotherapy, smoking, alcoholism, and other maladies. All these conditions underscore peripheral or central nervous system induced oxidative and nitrosative stress as the main common denominator. (Reviewed in Dunn 2007; Macdonald, Galley, Webster 2003; Milne et al. 2008; Moreira et al. 2007; Kücükakin et al. 2009; Stokes, Tailor, Granger 2005; Naoi et al. 2005; Jang et al. 2005). Altogether, there is a clear association and interaction of oxidative stress and depression, particularly if considered in light of new pharmacologic treatments against depression and neuroinflammatory load. On the other hand, since current antidepressants and anti-dementia or other neurodegenerative disease-directed therapeutic drugs still do not have the needed efficacy for a desired outcome, it is critical to: 1) – ascertain inflammation-depression and neurodegenerative (I-DND)-induced anti-oxidant drugs which may be combined with antidepressants; 2) – determine bio-markers for these interacting pathways (Maes et al. 2009) to target points of convergence; 3) – investigate gene expression, genotypes, and SNPs in the corresponding illnesses and determine the vulnerability of carriers to combined individual environmental, psychosocial and pathologic stresses in life by adjusting associated treatments to individual threshold potentials.

8. DO ALZHEIMER'S DISEASE AND MAJOR DEPRESSIVE DISORDER SHARE THE SAME OR SIMILAR SIGNALING PATHWAYS?

As shown above, clinicians have great difficulty in determining whether symptoms and signs of depression in elderly patients, particularly late onset depression, are originated either from this psychopathology or from dementia. This is particularly true when they find cognitive decrement symptoms as a comorbid entity. The main reason for this conundrum is that both psychiatric entities may share similar or analogous neural-biologic molecular signaling and processing. The interesting study of Wright and Persad (2007) presents a series of case studies to illustrate this challenge, and points out the importance in delineating treatments of both these illnesses. Many convergence factors or common points between MDD and AD are being currently studied. In addition to oxidative stress, corticotrophin releasing hormones, gonadotropin releasing hormones, and inflammation already discussed, some others will be briefly described below.

Brain derived neurotrophic factor

BDNF – is one of the most important survival factors in the brain; it is one of the nerve growth factor (NGF) family of proteins that help neurons and glia avoid damage, assist in cell repair, and is part of a series of signaling systems that confer neural resistance to internal or external insults to the CNS (Patapoutian and Reichardt 2001; Segal 2003). BDNF is widely distributed in the brain and is involved in transport, release, and binding to toxic agents constituting a robust defense system (Bregola et al. 2000). BDNF also mediates gene expression, eliciting responses that assist in many survival molecular strategies (Linholm et al. 1994). Finally, its positive actions in learning and memory, neurogenesis, synaptic transmission, brain electrical excitation inhibition, pain, and inflammation is beyond the scope of this report. BDNF is also essential to protect against neurodegeneration through

signaling pathways leading to cyclic AMP response element binding protein and stimulating DNA synthesis (Caccamo et al. 2010) through control of the amyloidogenic pathway and Aβ production in hippocampal neurons (Matrone et al. 2008) and through stimulating neural stem cells to improve cognition (blurton-Jones et al. 2009 Agonists of the BDNF receptor, tyrosine-receptor kinase B (TrkB) may imitate this growth factor, activating its receptor in the brain, inhibiting kainic acid-induced toxicity, decreasing infarct volumes in stroke and acting as a neuro-protective mediator in some neurodegenerative diseases. Jang et al (2010) provides evidence with a flavonoid agent, 7–8-dihydroxyflavone, that acts on TrkB showing its therapeutic potentials in AD. On the other hand, BDNF and other NGFs induce neurogenesis in the sub-granular-neuroproliferative zone of the dentate gyrus and CA1 region of Amon's horn in the adult brain (Kunkin et al. 2004). Indeed, neural stem cells, in a transgenic model of AD, may improve cognition through BDNF induction; BDNF addition, in recombinant forms, may mimic the beneficial effects of neural stem cell transplantation; and depletion does not increase hippocampal density nor improve cognition (Blurton-Jones et al. 2009). Turning to mood disorders, the work of Martinowich et al (2007) on BDNF function in depression and anxiety underscores that antidepressant drugs may up-regulate this survival protein. BDNF may have different functions in the brain based on a polymorphism in the region encoding the BNDF pro-domain leading to a valine at amino acid 66 being substituted by a methionine (Val66Met). The methionine allele in BNDF has been suggested to be protective for bipolar disorder and depression. The recent study of Terracciano et al (2011) establishes, in a large sample of 2,037 depressive patients, that plasma levels of BDNF are associated with neuroticism traits and depressive symptoms; BDNF level is inversely related to neurotic traces of personality, and lower BDNF concentrations may appear in severe depression. Furthermore, antidepressants chronically administered in depressive crises may up-regulate BDNF expression and infusion of BDNF into the hippocampus producing antidepressant effects and increasing adult hippocampal neurogenesis. Moreover, current research has directed attention to a possible "neurotrophin hypothesis of depression" which is based in great part on the associations of stress-depression syndromes or antidepressant treatments and down- or up-regulation of BDNF respectively (Martinowich et al. 2007). Research on the cell and molecular biology of BDNF are essential for the development of effective BDNF-based ADD and AD therapies (Woo et al. 2005).

From these studies we may suggest that the utility of BDNF in MDD and AD may lead to a strong competition between both illnesses for this survival factor: long term depression may induce AD development when there is an underlying genomic vulnerability for neurodegenerative illnesses; and conversely, depression may be induced by AD in case of genomic vulnerability to depression. In spite of the fact that biological mechanisms of this BDNF interaction are unknown, the rationale of this "competition" could explain the high incidence of AD in depression and the significantly higher incidence of depression in AD patients.

Neuropsychopharmacologic drugs and AD and MDD: interaction studies

It is interesting to note that current clinical treatments for both illnesses, Alzheimer's disease and most forms of depression disorders including anxiety and chronic stress, have produced

benefits using antidepressant drugs and some glutamate receptors antagonists. We will initially discuss the neuropsychopharmacology of the mood stabilizer drugs valproate and lithium. These medications have been extensively studied over the last decade, particularly their effects on triggering increased expression of cyto-protective and neurotrophic proteins such as bcl-2 in some regions of the central nervous system (Mangi 2000). This pro-survival transcription factor steadily increases its levels of neuroprotective effects; in lithium-treated mice a significant enrichment of hippocampal neurogenesis has been reported. Additionally, valproate may elevate neurite development and stimulates a signaling pathway – ERK mitogen-activated protein kinase, a molecular pathway utilized by many endogenous neurotrophic factors. Other clinical and neuroimaging studies are consistent with the neurotrophic and neuroprotective effects of these mood-stabilizer agents (Drevets 2000). This research group has demonstrated that chronic treatment with lithium or valproate either attenuate or reverse: the substantial gray matter reduction and decreased neuron density in pre-frontal cortex, the volume decrease of left nucleus accumbens-right putamen (Baumann et al. 1999; Rajkowska 2000; Vincent, Todtenkopf, Benes 1997), the reduction in specific layers enclosing the interneurons in the anterior cingulated cortex (Vincent, Todtenkopf, Benes 1997); the 40% volume decrease in non-pyramidal neurons in CA2 region of the hippocampal formation compared with control subjects; the 24% glial cells declined number in familial major depression and 41% in manic-depressive illness (Benes et al. 1998). Many pharmacological studies indicate that the therapeutic effects of these agents are due to structural changes in molecular level (Chen et al. 1999). Lithium mainly benefits cell survival: it induces an increase of B-cell lymphoma/leukemia-2 gene (Bcl-2) and reduction of glycogen synthase kinase-3β (GSK-3β). Bcl-2 protein protects neurons against many injuries, including oxidative stress (chemical oxidants) and long term ionizing radiation (Fugate). Furthermore, lithium was the first mineral agent that protected brain cells from premature death; and that may even cause brain cells to regenerate after a loss from disease (Moore 2000). The Wayne State University School of Medicine has also reported that, as lithium has high neurotrophic effects on neurons and glia survival, it should be investigated as a potential therapeutic drug for Alzheimer's and other neurodegenerative diseases that are characterized by the death of brain cells (Manji, Moore, Chen 1999; Manji, Moore, Chen 2000). In their studies of humans, rats, and brain cell cultures, these authors concluded that the increase in gray matter survival in neurons is about 220% more with lithium administration than in those of controls; and that gray matter volume enlarged by an average of 3%. Moreover, the action of lithium on AD may be assessed by its inhibitor action on GSK-3β causing reduced tauopathy and neurodegenerative effect (Noble et al. 2005), and its indirect action should be investigated in manic-depression associated with AD to determine whether patients with manic-depression that receive lithium have a decreased incidence of AD. The effects of lithium are still not clearly understood due to the complexity of its molecular mechanisms of action, including its influence on signal transduction and transcriptional factors, contributing to neuroplasticity; the blocking of many other kinases besides GSK-3β; and indirectly, inducing the attenuation of tau phosphorylation (Lenox and Hahn 2000) reducing neurofibrillary tangles (NFTs).

For more than a decade, antidepressants have been thought to have an attenuated action on stress-induced alterations in brain metabolism, hippocampal volume and cell proliferation

(Czéh et al. 2001; Gould et al. 1998; Sapolsky 2001), particularly in acute syndromes (Holsboer et al. 1995). In summary, the lithium-antidepressant effects in AD and MDD include: 1 - Alzheimer's disease is correlated with high cortisol levels, hippocampal atrophy and impaired hippocampal metabolism with reduction of neurogenesis through apoptosis and necrosis. 2 – chronic treatment with therapeutic lithium concentrations or other antidepressant drugs may favor neurogenesis, decrease the vulnerability of brain cells to oxidative stress, induce post-translational changes in molecular chaperones, decrease production of amyloid-β, inhibit Aβ-induced stress, prevent tau phosphorylation, and exert neuroprotective effects by increasing resistance to oxidative damages. 3 - Lithium may prevent protein misfolding and accumulation of AD associated cytotoxic aggregates, increasing expression of heat shock proteins (HSPs) and/or protecting chaperones (Allagy et al. 2009); and antidepressant drugs may up-regulate BDNF (Martinowich, Manji, Lu 2007; Terracciano et al. 2011), invoking the "neurotropic hypothesis of depression" (Martinowich, Manji, Lu 2007; Terracciano et al. 2011; Woo et al. 2005). Other neuropychopharmacological studies have been done in the last 20 years on the dual effects of NMDARs antagonists, which may confirm the intimate interaction of the molecular pathogenic mechanisms of MDD and AD. In fact, many studies have shown that memantine (Reisberg et al. 2003), a non-competitive NMDAR antagonist, broadly used as a therapeutic agent in moderate to severe AD, and other similar agents such as amantadine, bifemelane (Mory, Danysz, Quack 1993) and ketamine (Berman et al. 2000) may have potential antidepressant properties in depressed patients with either associated or unassociated AD. Moreover, significant therapeutic interactions between these non-competitive NMDAR antagonists (amantadine, neramexane or memantine) with the antidepressants imipramine, fluoxetine, and/or venlafaxine – used in the forced swimming test model in rats - were more effective in treating depression than antidepressants alone, suggesting a new integrated therapeutic use for anti-depressant resistant patients (Rogóz et al. 2002). The NMDAR antagonists were also effective in humans in diseases of aging (Le and Lipton 2001). Finally, the interesting study of Paul and Skolnick (Paul and Skolnick 2003) on glutamate, NMDA receptor, and AMPA receptor effects on depression and suicide symptoms to promote more effective antidepressant treatments in anxiety-depressive patients indicates that the use of integrated excitatory amino acids antagonists and antidepressants in depressive patients is already a reality.

GSK-3β, Heat shock proteins, and Heme-oxygenase

GSK-3β has essential roles in the brain, affecting synaptic plasticity, neurogenesis, and cell adhesion, among others. The importance of this kinase for understanding the interaction between a series of molecular pathways in either AD or MDD is relevant. A few brief illustrations are presented below: GSK-3β phosphorylates tau protein and impairs its anti-apoptotic effect through competition with β-catenin which, when dephosphorylated, increases resistance to apoptosis leading to phosphorylated tau-induced neuronal necrosis in neurodegenerative diseases (Ii et al. 2007). GSK-3β is a pathological feature of AD in many other processes and may be activated by the intracellular domain of AβPP. Patients with elevated levels of amyloid intracellular domain show, through GSK-3β hyper-activation, pathological and clinical signs of AD (Ghosal et al. 2009). Inhibition of GSK-3β by many therapeutic agents such as lithium induces a decrease in pathological tau levels and

attenuates degeneration of neurons and glia in AD (Noble et al. 2005). In depression-stress-anxiety phenotypes, GSK-3β is disinhibited by attenuation of the survival pathway BDNF-PI3-K/Akt that inhibits it (Del Rio and Frenchilla 2006). Hyperphosphorylation, a mark of GSK-3β, then goes forward and may act to induce AD (Ghosal et al. 2009; Ii et al. 2007). GSK-3β inhibitors, lithium and other agents display anti-manic and antidepressant effects in some animal models. However, the mechanisms by which attenuation of depression and mania occurs are unknown (Du et al. 2010). GSK-3β is a potential pathologic agent in the development of either AD or MDDs; as such it is currently an important target for investigations of inhibitory agents to include and improve the new integrated therapies of AD and MDD (Bhat, Budd Haeberlein, Avila 2004).

On the other hand, heat shock proteins (HSPs), currently known as heat shock factors (HSFs), have been shown to be key participants in many cellular pathways involved in the protection against ONS in particular brain regions (Calabrese et al. 2003). The major proteins of the HSP family (HSP-70, HSP-60, HSP-27, ubiquitin) are known as functional chaperones, which trigger pathways involved in the “unfolded protein stress response.” They protect neurons from oxidative stress, degrading the toxic heme into free iron, carbon monoxide, and the antioxidant bilirubin (Doré et al. 1999). The heat shock protein-32 (HSP-32) or heme oxygenase (HO-1/HO-2) is known also as a vita-gene - a protein originated in genes that protect survival - and is a robust anti-oxidant and modulator of the onset and progression of major neurodegenerative disorders such as AD and PD, through the molecular mechanisms reported in (Doré et al. 1999). The activation of HO-1, thioredoxin (TRX), other detoxifying enzymes (Mn-SOD, GSH-Px, NADPH, CAT), cytokine immunoreceptors and growth factors that constitute the “vita-gene system” by the slow accumulation of free radicals from metabolism, aging or pathological conditions, is part of strong defense mechanisms against disease and aging in the brain. The pro-survival mechanism controlled by the homeodynamic “vita-gene system” acts as a series of molecular defenses against brain diseases through modulation of ROS and RNS, attenuating brain oxidative stress (Calabrese et al. 2007). Since oxidative stress has a solid association with AD, this “vita-gene protection system” may also be related or associated with neuronal damage provoked by the chronic stress-depression-anxiety diseases (Calabrese et al. 2007).

Redox transition metals

Many studies have been done on the participation of iron and copper in neurodegenerative diseases, particularly Parkinson’s and Alzheimer’s, with the induction of early and continuous oxidative stress damage (Huang et al. 1999; Nunomura et al. 2001; Perry et al. 2000; Perry et al. 2002). These studies support the utility of investigation into the clearance of redox metals from the brain and the therapeutic applications thereof. The purported role of Aβ accumulation is not consistent with many clinical and pathological phenotypes currently found (Perry et al. 2000; Smith et al. 2002), the functions of iron-monomeric Aβ-ApoEε4 binding (Rodrigues et al. 2010); and of early defenses against oxidative stress from the beginning of AD (Nunomura et al. 2001). There are almost no reports on the direct participation of these transition redox metals in chronic-anxiety-depression stress diseases. Meanwhile, single nucleotide polymorphisms in some haplotypes tagged depression-stress related (Peters et al. 2004) or in individual specific genes (Canli et al. 2005) are increasingly

being investigated as phenotypic inducers of antidepressant treatment responses. An important study on this topic, likely based on the previous studies of the association of the human serotonin transporter genotypes and neurobehavioral disorders, has recently been reported. Based on a transgenic inbred mouse strain, serotonin transporter knock out lines harboring complex haplotypes, it has been shown that serotonin transporter-dependent 5-HT signaling is a major determinant of midbrain iron homeostasis, a condition which, in turn, dictates iron-regulated DA neuropsychiatric phenotypes, including alcohol consumption and depression-anxiety behaviors (Carneiro et al. 2009). These findings establish that serotonin transporter genotypes, which have been related to low anxiety, dysthymia and depression-stress behaviors phenotypes (Cairo et al. 2002; Carneiro et al. 2009; Holmes et al. 2003; Jennings et al. 2006), do not yet have clear interactions with these neuropsychiatric DA and serotonin-dependent symptoms via iron homeostasis regulation. In view of the fact that redox transition metals are deeply involved in AD (Huang et al. 1999; Perry et al. 2002), metal interaction in MDD and related disorders should be thoroughly investigated.

DISCUSSION

Our review focuses on oxidative stress as the central point of convergence between MDD and AD. As a first approach it was shown that 30% – 50% of AD individuals have a previous history or express signs and symptoms of the depression spectra. This leads to the question of whether oxidative stress - a critical element in the development of AD – also induces the major neural pathology found in depression, particularly in the hippocampus and pre-frontal cortex. The following consideration was that in genomic vulnerability to depression; psychosocial stress, severe life threatening events, or mental and/or affective somatic disease stresses may originate an alternate phenotype through activation of the HPA axis, resulting in CRHs increased brain concentrations and reinforced by arginine vasopressin and gonadotropin releasing hormone (GRH) co-expression. The induction of elevated glutocorticoid levels damages the limbic neurons, which leads to hippocampal atrophy and surplus release of corticoid releasing hormones, closing the circle. Next, we suggest that the serendipitously established excitatory amino acid activation and intracellular Ca^{2++} influx accelerate the increased oxidative metabolism and free radical formation promoting the “oxidopamatergic” cascade which boosts the glucocorticoid cascade in the neurotoxic effects. Surprisingly, we found that the glucocorticoid and oxidopamatergic cascades - paralleled by some specific antioxidant defenses such as increasing Aβ aggregation, tau hyper-phosphorylation and impaired ApoEε4 function in genomic vulnerability to AD individuals - lead to the AD spectra and are either similar to or the same as those in the depressive phenotype. We have also shown that inflammatory phenotypes and elevation of cytokine levels in brain are also sub-central factors influencing signaling all along the MDD/AD spectra. The cytokines associated with either or both illnesses are yet not clear as it is not known which of the associated phenotypes are first expressed. Nonetheless, oxidative stress is involved in the ubiquitous manifestation of inflammation/cytokines, pervasively activating the hypothalamic pituitary adrenal and arginine vasopression systems and reinforcing psychosocial stress, severe life threatening events, and mental/affective somatic diseases induced glucocorticoid cascades, arginine vasopressin, oxidative damage, and estrogen cascades. Interestingly, we found that these cascades are

similar or the same in either MDD or AD spectra, which may be differentiated only by the origin of the genomic vulnerability. As a final step, we briefly mention some of the other molecular intermediates of convergent points between these pathologies, underlining the use of neuro-psychopharmacology to confirm that positive results may be obtained using similar drugs to treat either disease. Other convergent signaling by some molecular pathways, BDNF, GSK-3β, HSPs/HO-1, and redox transition metals were discussed with the purpose of reinforcing our proposal.

In Figure 1 we present a simple diagram through which we endeavor to summarize the main aspects of our review.

CONCLUSION

In Figure 2 we summarize our hypothesis, emphasizing the molecular cascades which, along all the diseases' development, accumulate the OS burden leading to MDD or AD. The pathway depends on the genomic vulnerability to depression and/or Alzheimer's disease, respectively. In both illnesses psychosocial stress, severe life threatening events, and/or mental-affective somatic disorders may provoke robust stimulation of the brain molecular oxidation cascades (defenses, which go downstream to glucocorticoid, "oxidopamatergic", and cytokines inflammatory cascades). The free radical formation from these continuing long term life molecular cycles lead to oxidative stress if those molecular cascades overload the brain's naturally constituted genomic threshold. In individuals with genomic vulnerability to depression, depression cascades; whereas alternately, in subjects with genomic vulnerability to Alzheimer's disease, AD cascades advance to MMD and/or AD respectively. These pathologic phenotypes close the cycle, leaving environmental, internal life stresses, and genomic vulnerabilities as the "decision" about which pathways will be followed during brain aging. This proposal is consistent with the lack of any strictly identifying molecular phenotype changes between MDD or AD, besides their genomic vulnerability.

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ABBREVIATIONS

AD	Alzheimer's disease
Aβ	amyloid-β
ACTH	adrenal corticotrophic hormone
AGE	advanced glycation end product
ApoEε4	apolipoprotein Eε4
AβPP	amyloid β protein precursor

BDNF	brain derived neurotrophic factor
CSF	cerebral spinal fluid
DNA	deoxyribonucleic acid
GSK-3β	glycogen synthase kinase-β
GRH	gonadotropin releasing hormone
G-Px	glutathione peroxidase
4-HNE	4-hydroxy-nonenal
HSP	heat shock protein
5-HTT	serotonin transporter
IL-1β	interleucine-1β
IFN-γ	interferon-γ
IL-1	interleukin-1
IL-6R	interleukin-6 receptor
JAK	Janus kinase
JNK 1–3	Jun NH2 kinases 1–3
MAPK	mitogen activated protein kinase
MCI	mild cognitive impairment
MDD	major depressive disorder
NGF	nerve growth factor
NFT	neurofibrillary tangle
NMDA	n-methyl-dextro-aspartate
NMDAR	NMDA receptor
NO	nitric oxide
NSAID	non steroidal anti-inflammatory drugs
NSD	not senile dementia
PET	positron emission tomography
PKC	protein kinase C
RNS	reactive nitrogen species
ROS	reactive oxygen species
SDAT	senile dementia of Alzheimer type
SP	senile plaque
Tau	tau protein

TNF-α tumor necrosis factor-α TRK-β, tyrosine receptor kinase-β

References

Akiskal, HS.; Lewis, LJ. The depressive spectrum: re-conceptualizing the relationship between dysthymic, sub-threshold and major depressions. In: Licinio, J.; Wong, M-L., editors. Biology of depression: from novel insights to therapeutic strategies. Wiley-VCH Verlag GmbH & Co., Weinheim GmbH & Co; Weinheim: 2005. p. 47-70.

Akiskal HS, McKinney WTJ. Depressive disorders: toward a unified hypothesis. Science. 1973; 182:20–29. [PubMed: 4199732]

Alexopoulos G, Young R, Meyers B. Geriatric depression: age of onset and dementia. Biol Psychiatry. 1993; 1934:141–145. [PubMed: 8399805]

Allagy MS, Nciri R, Rouhayd MF, Mourat GC, El Feki A, Croute D, Vincent C. Long term exposure to low lithium concentrations stimulates proliferation, modifies stress protein expression pattern and enhances resistance to oxidative stress in SH-SY5Y cells. Neurochem Res. 2009; 34:453–462. [PubMed: 18688712]

Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotrophin-releasing factor in depression and anxiety disorders. J Endocrinol. 1999; 160:1–12. [PubMed: 9854171]

Atwood CS, Meethal SV, Liup T, Wilson AC, Gallego M, Smith MA, Bowen RL. Dysregulation of the hypothalamic-pituitary-gonadal axis wit menopause and andropause promotes neurodegenerative senescence. J Neuropathol Exp Neurol. 2005; 64:93–103. [PubMed: 15751223]

Author-Kokmen E, Beard CM, Chandra V, Offord KP, Schoenberg BS, Ballard DJ. Clinical risk factors for Alzheimer's disease: a population-based case-control study. Neurol. 1991; 41:1393–1397.

Avshalumov MV, Rice ME. Activation of ATP-sensitive K+ c(KATP) channels by H2O2 underlies glutamate-dependent inhibition of striatal dopamine release. Proc Natl Acad Sci U S A. 2003; 100:11729–11734. [PubMed: 13679582]

Ballmaier M, Narr KL, Toga AW, Elderkin-Thompson V, Thompson PM, Hamilton L, Ebrahim H, Pham D, Heinz A, Kumar A. Hippocampal morphology and distinguishing late-onset from early-onset elderly depression. Am J Psychiatry. 2008; 165:229–237. [PubMed: 17986679]

Ballmaier M, Narr KL, Toga AW, Elderkin-Thompson V, Thompson PM, Hamilton L, Haroon E, Pham D, Henz A, Kumar A. Hippocampal morphology and distinguishing late-onset from early onset elderly depression. Am J Psychiatry. 2008; 165:229–237. [PubMed: 17986679]

Bao AM, Fischer DF, Wu Y-H, Hol EM, Balsear R, Unmehopa UA, Zhou JN, Swaab DF. A direct androgenic involvement in the expression of human corticotrophin releasing hormone. Mol Psychiatry. 2006; 11:567–576. [PubMed: 16446741]

Bao A-M, Meynen G, Swaab DF. The stress system in depression and neurodegeneration: focus on the hypothalamus. Brain Res Rev. 2008; 57:531–553. [PubMed: 17524488]

Bao A-M, Meynena G, Swaab DF. The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res Rev. 2008; 57:531–553. [PubMed: 17524488]

Bao AM, Swaab DF. Gender difference in age-related number of corticotrophin–releasing hormone-expressing neurons in the human hypothalamic paraventricular nucleus and the role of sex hormones. Neuroendocrinology. 2007; 95:27–36. [PubMed: 17308368]

Baumann B, Danos P, Krell D, Diekmann S, Leschinger A, Stauch SR, et al. Reduced volume of limbic system-affiliated basal ganglia in mood disorders: preliminary data from a post mortem study. J Neuropsychiatry Clin Neurosci. 1999; 11:18071–18078.

Baumann, MH.; Rothman, RB. Neurobiology of 3–4-Methylenedioxy-methamphetamine MDMA, or "Ecstasy. In: Karch, SB., editor. Neurochemistry of Abused Drugs. CRC Press Taylor & Francis Group; Boca Raton, FL: 2008. p. 119-142.

Behl C, Lezoualch F, Trapp T, Widmann, Skutella T, Holsboer F. Glucocorticoids enhance oxidative stress-induced cell death in hippocampal neurons in vitro. Endocrinol. 1997; 13891:101–105.

Benes FM, Kwok EW, Vincent SL, Todtenkopf MS. A reduction of not-pyramidal cells in sector CA2 of schizophrenics and manic depressives. Biol Psychiatry. 1998; 44:88–97. [PubMed: 9646890]

Berman RM, Capiello A, Anand A, Oren DA, Henninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000; 47:351–354. [PubMed: 10686270]

Bhat RV, Budd Haeberlein SL, Avila J. Glycogen synthase kinase-3: a drug target for CNS therapies. J Neurochem. 2004; 89:1313–1317. [PubMed: 15189333]

Bilici M, Efe H, Koroglu MA, Uydu HA, Bekaroglu M, Deger O. Anti-oxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. J Affect Disord. 2001; 64:43–51. [PubMed: 11292519]

Bindoli A, Rigobello MP, Deeble DJ. Biochemical and toxicological properties of the oxidation products of catecholamines. Free Radic Biol Med. 1992; 13:391–405. [PubMed: 1398218]

Bitran D, Shiekh M, Dowd A, Dugan MM, Renda P. Corticosterone is permissive to the anxiolytic effect that results from the blockade of hippocampal mineralocorticoid receptors. Pharmacol Biochem Behav. 1998; 60:879–887. [PubMed: 9700972]

Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Müller F-J, Loring JF, Yamasaki TR, Poon WW, Green KN, LaFerla LM. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci U S A. 2009; 106:13594–13599. [PubMed: 19633196]

Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Müller F-J, Loring JF, Yamasaki TR, Poon WW, Green KN, LaFerla FM. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci U S A. 2009; 106:13594–13599. [PubMed: 19633196]

Bregola, et al. Different patterns of induction of fibroblast growth factor-2 and brain-derived neurotrophic factor messenger RNAs during kindling epileptogenesis and development of a herpes simplex vector for fibroblast growth factor-2 gene transfer in vivo. Epilepsia. 2000; 419:s122–s126. [PubMed: 10999533]

Bremner DJ. Does stress damage the brain? Biol Psychiatry. 1999; 45:797–805. [PubMed: 10202566]

Brown GW, Harris TO, Hepworthy C. Life events and endogenous depression: a puzzle re-examined. Arch Gen Psychiatry. 1994; 51:525–534. [PubMed: 8031225]

Caccamo A, Maldonado MA, Bokov AF, Majumder S, Oddo S. CBP (CREB binding protein) gene transfer increases BDNF levels and ameliorates learning and memory deficits in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. 107:22687–22692. [PubMed: 21149712]

Caine ED. "Pseudo-dementia": current concepts and future directions. Arch Gen Psychiatry. 1981; 38:1359–1364. [PubMed: 7316680]

Cairo G, Recalcati S, Pietrangelo A, Minotti G. The Iron regulatory proteins: targets and modulators of free radical reactions and oxidative damage. Free Radic Biol Med. 2002; 32:1237–1243. [PubMed: 12057761]

Calabrese, B.; Mancuso, C.; De Marco; Giuffrida, S.; Butterfield, DA. Nitric oxide and cellular stress response in brain aging and neurodegenerative disorders. In: Qureshi, GA.; Parvez, SH., editors. Oxidative stress and neurodegenerative disorders. Elsevier; Amsterdam: 2007. p. 115-134.

Calabrese B, Scapagnini G, Colombrita C, Ravagna A, Pennisi G, Giuffrida Stella AM, Galli F, Butterfield DA. Redox regulation of heat shock protein expression in aging and neurodegenerative disorders associated with oxidative stress: a nutritional approach. Amino Acids. 2003; 25:437–447. [PubMed: 14661103]

Calabrese V, Guagliano E, Sapienza M, Panebianco M, Calafao S, Puleo E, Pennisi G, Mancuso C, Butterfield DA, Stella AG. Redox regulation of cellular stress responses in aging and neurodegenerative disorders: role of vita-genes. Neurochem Res. 2007; 32:757–773. [PubMed: 17191135]

Calapai G, Crupi A, Firenzuoli F, et al. Interleukin-6 involvement in antidepressant action of Hypericum Perforatum. Pharmacopsychiatry. 34(Suppl 1):S8–S10. [PubMed: 11518082]

Canli T, Omura K, Haas BW, Fallgatter A, Constable RT, Lesch KP. Beyond affect: a role for genetic variation of the serotonin transporter in neural activation during a cognitive attention task. Proc Natl Acad Sci U S A. 2005; 102:12224–12229. [PubMed: 16093315]

Carneiro AMD, Airey DC, Thompson BA, Zhu C-B, Lu L, Erikson KM, Blakely RD. Functional coding variation in recombinant inbred mouse lines reveals multiple seroronin transporter-associated phenotypes. Proc Natl Acad Sci U S A. 2009; 106:2047–2052. [PubMed: 19179283]

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, McClay J, Harrington H, Mill J, Martin J, Braithwaite A, Pouton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003; 301:386–389. [PubMed: 12869766]

Catena-Dell'Osso M, Bellantuono C, Consoli G, Baroni S, Rotella F, Marazziti D. Inflammatory and neurodegenerative pathways in depression: a new avenue for antidepressant development? Curr Med Chem. 2011; 18:245–255. [PubMed: 21110802]

Chalmers DT, Desar D, Graham DI, Brooks DN, McCulloch J. Differential alterations of cortical glutamatergic binding sites in senile dementia of the Alzheimer type. Proc Natl Acad Sci U S A. 1990; 87:1352–1356. [PubMed: 2154742]

Chalmers DT, Desar D, Graham DI, Brooks DN, McCulloch J. Differential alterations of cortical glutamatergic binding sites in senile dementia of the Alzheimer type. Proc Natl Acad Sci U S A. 1990; 87:1352–1356. [PubMed: 2154742]

Chen G, Zeng WZ, Jiang L, Yuan PX, Zhao J, Mangi HK. The mood-stabilizing agents lithium and valproate robustly increase the expression of the neuroprotective protein Bcl-2 in the CNS. J Neurochem. 1999; 72:879–882. [PubMed: 9930766]

Chen KH, Reese EA, Kim H-W, Rapoport SI, Rao JS. Disturbed neurotransmitter transporter expression in Alzheimer's disease brain. J Alzheimers Dis. 2011; 26:755–766. [PubMed: 21743130]

Coppedè, F.; Migliore, L. Genetic and environmental factors in neurodegenerative diseases. In: Qureshi, GA.; Parvez, SH., editors. Oxidative stress and neurodegenerative disorders. Elsevier; Amsterdam: 2007. p. 89-114.

Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. Science. 1993; 262:689–695. [PubMed: 7901908]

Czéh B, Michaelis T, Watanabe T, Frahm J, Biurrun G, van Kampen M, Gartolomucci A, Fuchs E. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci U S A. 2001; 98:12796–12801. [PubMed: 11675510]

Davis JB, Maher P. Protein kinase C activation inhibits glutamate induced cytotoxicity in a neuronal cell lines. Brain Res. 1994; 652:169–173. [PubMed: 7953717]

Davis KL, Davis BM, Greenwald BS, Mohs RC, Mathe AA, Johns CA, Horvath TB. Cortisol and Alzheimer's disease, I:Basal Studies. Am J Psychiatry. 1986; 143:300–305. [PubMed: 3953862]

De Kloet ER, Reul JMHM. Feedback action and tonic influence of corticosteroids on brain function: a concept arising from the heterogeneity of brain receptor systems. Psychoneuroendocrinology. 1987; 12:83–105. [PubMed: 3037584]

De Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. Endocrinol Rev. 1998; 19:269–301.

de Leon MJ, George AE, Golomb C, Tarshish A, Convit A, Lluger S, De Santi T, Mc Rae SH, Ferris B, Reisberg C, Ince H, Rusinek M, Bobinski B, Quinn B, Miller DC, Wisniewski HM. Frequency of hippocampal formation atrophy in normal aging and Alzheimer's disease. Neurobiol Aging. 1997; 18:1–11. [PubMed: 8983027]

de Leon MJ, George AE, Stylopoulos LA, Smith G, Miller DC. Early marker for Alzheimer's disease: the atrophic hippocampus. Lancet. 1989; 2:672–673. [PubMed: 2570916]

Del Rio, J.; Frenchilla, D. Glutamate and depression. In: Schmidt, WJ.; Reith, MEA., editors. Dopamine and glutamate in psychiatric disorders. Humana Press; Totowa, New Jersey: 2006. p. 215-236.

Devenand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. Arch Gen Psychiatry. 1996; 53:175–182. [PubMed: 8629893]

Doré S, Takahashi M, Ferris CD, Hester LD, Guastella D, Snyder SH. Bilirubin, formed by activation of heme oxygenase-2, protects neurons against oxidative stress injury. Proc Natl Acad Sci U S A. 1999; 96:2445–2450. [PubMed: 10051662]

Drevets WC. Neuroimaging studies of mood disorders. Biol Psychiatry. 2000; 48:813–829. [PubMed: 11063977]

Du J, Wei Y, Liu L, Wang Y, Khairova R, Blumenthal R, Tragon T, Hunsberger JG, Machado-Vieira R, Drevets W, Wang YT, Manji HK. A kinesin signaling complex mediates the ability of GSK-3β to affect mood-associated behaviors. Proc Natl Acad Sci U S A. 2010; 107:11573–11578. [PubMed: 20534517]

Dunn, AJ. Cytokines, stress, and depression. In: Plotnikoff, NP.; Faith, RE.; Murgo, AJ.; Good, RA., editors. Cytokines, stress And immunity. Taylor & Francis Group; Boca Raton, New York: 2007. p. 193-214.

Engelhardt E, Laks J, Cavalcanti JLS. The glutamatergic system and Alzheimer's disease. Braz Rev Neurol. 2003; 39:5–21.

Ereb I, Naziroglu M, Demirdas A. Protective effects of lamotrigine, aripiprazole and escitalopram on depression-induced oxidative stress. Neurochem Res. 2007; 32:1188–1195. [PubMed: 17401662]

Eren I, Nazıroğlu M, Demirdaş A, Çelik ÖA, Uğuz Ci, Altunbaşak A, Özmen I, Efkan Uz. Venlafaxine modulates depression-induced oxidative stress in brain and medulla of rat. Neurochem Res. 2007; 32:497–505. [PubMed: 17268845]

Eriksson PS, Permilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. Nat Med. 1998; 4:1313–1317. [PubMed: 9809557]

Erkut ZA, Pool G, Swaab DF. Glucocorticoids suppress corticotropin-releasing hormone and vasopressin expression in human hypothalamic neurons. J Clin Endocrinol Metab. 1998; 83:2066–2073. [PubMed: 9626140]

Fiebich BL, Hollig A, Lieb K. Inhibition of substance P-induced cytokine synthesis by St. John's Wort extracts. Pharmacopsychiatry. 2001; 34(Suppl 1):S26–S28. [PubMed: 11518071]

Fonum F. Glutamate: a neurotransmitter in mammalian brain. J Neurochem. 1984; 42:1–11. [PubMed: 6139418]

Fugate, L. [Accessed 10 June 2013] Lithium's potential role in preventing Alzheimer's disease. Mineral benefits other conditions besides bipolar disorder. http://intelegen.com/nutrients/lithium.htm

Gazzaley AH, Weiland NG, McEwen BS, Morrinson JH. Differential regulation of NMDAR-I mRNA and protein by estradiol in the rat hippocampus. J Neurosci. 1996; 16:6830–6838. [PubMed: 8824322]

Geerlings MI, Schoevers RA, Beekman ATF, Jonker C, Deeg DJH, Schmand B, Adèr HJ, Bouter LM, Van Tilburg W. Depression and risk of cognitive decline and Alzheimer's disease: results of two prospective community-based studies in The Netherlands. Brit J Psychiatry. 2000; 76:568–5754. [PubMed: 10974964]

Geerlings, den Heijer T, Koudstaal PJ, Hofman A, Breteler MMB. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer's disease. Neurol. 2008; 70:1258–1264.

Ghosal K, Vogt DL, Liang M, Shen Y, Lamb BT, Sanjay WP. Alzheimer's disease-like pathological features in transgenic mice expressing the APP intracellular domain. Proc Natl Acad Sci U S A. 2009; 106:18367–18372. [PubMed: 19837693]

Gille, G.; Riederer, P. Dopamine and neurodegeneration. In: Schmidt, WJ.; Reith, MEA., editors. Dopamine and glutamate in psychiatric disorders. Humana Press; Totowa, New Jersey: 1995. p. 415-445.

Goodman Y, Bruce AJ, Cheng B, Mattson MP. Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid β-peptide toxicity in hippocampal neurons. J Neurochemi. 1996; 66:1836–1844.

Gorczynski, R.; Stanley, J. Biological activities of cytokines that signal via the JAK/STAT pathway. In: Gorczynski, R.; Stanley, J., editors. Clinical immunology: an introductory text. Landes Bioscience; Jorgetown, Texas: 1999. p. 117-120.

Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A. 1998; 95:3168–3171. [PubMed: 9501234]

Green RCL, Cupples A, Kurz A, Auerbach S, Go R, Sadovnick D, Duara R, Kukull WA, Chui H, Edeki T, Griffith PA, Friedland RP, Bachman D. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Arch Neurol. 2003; 60:753–759. [PubMed: 12756140]

Greene JG, Greenamyre JT. Exacerbation of NMDA, AMPA and L-glutamate excitotoxicity by the succinate dehydrogenase inhibitor malonate. J Neurochem. 1995; 64:2332–2338. [PubMed: 7536810]

Gruenberg, AM.; Goldstein, RD.; Pincus, HA. Classification of depression: research and diagnostic criteria: DSM-IV and ICD-10. In: Licinio, J.; Wong, M-L., editors. Biology of Depression: From Novel Insights to therapeutic Strategies. Wiley-VCJ Verlag GmbH & Co; Weinheim: 2005. p. 1-12.

Gudelsky GA, Yamamoto BK. Neuropharmacology and neurotoxicity of 3,4-methylene-dioximethamphetamine (MDMA). Methods Mol Med. 2003; 79:55–73. [PubMed: 12506690]

Gwag BJ, Lobner D, Koh JY, Wie MB, Choi DW. Blockade of glutamate receptors unmasks neuronal apoptosis after oxygen-glucose deprivation in vitro. Neurosci. 1995; 68:615–619.

Haines, JL.; Bailey, LR.; Grubber, JM.; Hedges, D.; Hall, JL.; West, S.; Santoro, L.; Kemmerer, B.; Sauders, A.; Roses, AD.; Small, GW., et al. A genomic search for Alzheimer's disease genes. In: Iqbal, K.; Sisodia, S.; Winblad, B., editors. Alzheimer's disease: advances in etiology, pathogenesis and therapeutics. John Wiley & Sons Ltd; 2000. p. 33-45.

Halliwell, B.; Gutteridge, JMC. Free radicals in biology and medicine. New York: Oxford; 1993.

Hartmann A, Veldhuis JD, Deuschle M, Standhardt H, Heuser I. Twenty-four hour cortisol release profiles in patients with Alzheimer's and Parkinson's disease compared to normal controls: ultradian secretory pulsatility and diurnal variation. Neurobiol Aging. 1997; 18:285–289. [PubMed: 9263193]

Hattori A, Luo Y, Umegaki H, Munoz J, Roth GS. Intrastriatal injection of dopamine results in DNA damage and apoptosis in rats. Neuroreport. 1998; 9:2569–2572. [PubMed: 9721934]

Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci. 1997; 20:78–84. [PubMed: 9023876]

Herman JP, Patel PD, Akil H, Watson SJ. Localization and regulation of glucocorticoid and mineralocorticoid receptor messenger RNAs in the hippocampal formation of the rat. Mol Endocrinol. 1989; 3:1886–1894. [PubMed: 2558306]

Holmes A, Lit Q, Murphy DL, Gold D, Crawley JN. Abnormal anxiety-related behavior in serotonin transporter null mutant mice: the influence of genetic background. Genes Brain Behav. 2:365–380. [PubMed: 14653308]

Holsboer F, Lauer CJ, Schreiber W, Krieg J-C. Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familiar risk for affective disorders. Neuroendocrinology. 1995; 62:340–347. [PubMed: 8544947]

Hoogendijk WJG, Meynen G, Endertc E, Hofman MA, Swaab DF. Increased cerebrospinal fluid cortisol level in Alzheimer's disease is not related to depression. Neurobiol Aging. 2006; 27:780.e1–780.e2. [PubMed: 16198445]

Huang X, Awood CS, Hartshorn MA, et al. The Aβ peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. Biochem. 1999; 38:7609–7616. [PubMed: 10386999]

Issa AM, Rowe W, Gauthier S, Meaney MJ. Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. J Neurosci. 1990; 10:3247–3254. [PubMed: 2170594]

de Haan, JB.; Crack, PJ.; Pritchard, MA.; Kola, I. Down syndrome, antioxidant balance and the "gene dosage effect" hypothesis. In: Qureshi, GA.; Parvez, HS., editors. Oxidative stress and neurodegenerative disorders. Elsevier; Amsterdam, Boston: 2007. p. 219-236.

Jacobson L, Sapolski RM. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenal axis. Endocr Rev. 1991; 12:118–134. [PubMed: 2070776]

Jang SW, Liu X, Yepes M, Shepherd KR, Miller GW, Liu Y, Wilson WD, Siao g, Blanchi B, Sun YE, Ye K. A selective TrkB agonist with potent neurotrophic activities by 7—dihydroxyflavone. Proc Natl Acad Sci U S A. 2010; 107:2687–2692. [PubMed: 20133810]

Jang, J-H.; Surh, Y-J. Implications of inflammatory stress in Alzheimer's disease. In: Packer, L.; Surh, Y-J., editors. Oxidative stress, inflammation and health. Taylor and Francis Group; Boca Raton: 2005. p. 445-470.

Jellinger, KA. Advances in our understanding of neurodegeneration. In: Qureshi, GA.; Parvez, SH., editors. Oxidative stress and neurodegenerative disorders. Elsevier; Amsterdam: 2007. p. 1-58.

Jellinger, KA. Advances in our understanding of neurodegeneration. In: Parvez, SH.; Qureshi, AG., editors. Oxidative stress And neurodegenerative disorders. Elsevier; Amsterdam, Boston: 2007. p. 1-58.

Jennings KA, Loder MK, Sheward WJ, Pei Q, Deacon RMJ, Benson MA, Olverman HJ, Hastie ND, Harmar AJ, Shen S, Sharp T. Increased expression of the 5-HT transporter confers a low-anxiety phenotype linked to decreased 5-HT transmission. J Neurosci. 2006; 26:8955–8964. [PubMed: 16943551]

Jimenez DR, Velez PC, Pinxteren J, De Potter W, Ebinger G, Vauquelin G. Binding of serotonin and dopamine to 'serotonin binding proteins' in bovine frontal cortex: evidence for iron-induced oxidative mechanisms. Eur J Pharmacol. 1993; 247:11–21. [PubMed: 8258356]

Kaltschmidt PA, Uherek M, Volk B, Baeuerle PA, Kaltschmidt C. Transcriptor factor NF-kβ is activated in primary neurons by amyloid-β peptides and in neurons surrounding early plaques from patients with Alzheimer's disease. Proc Natl Acad Sci U S A. 1997; 94:2642–2647. [PubMed: 9122249]

Kessing LB, Nilsson FM. Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord. 2003; 73:261–269. [PubMed: 12547295]

Khan TK, Alkon DL. An internally controlled peripheral biomarker for Alzheimer's disease: Erk1 and Erk2 responses to the inflammatory signal bradikinin. Proc Natl Acad Sci U S A. 2006; 103:13203–13203. [PubMed: 16920798]

Koo, Ko; Russi, JW.; Ferguson, D.; Nestler, EJ.; Duman, RS. Nuclear factor – kβ is a critical mediator of stress-impaired neurogenesis and depressive behavior. Proc Natl Acad Sci U S A. 2010; 107:2669–2674. [PubMed: 20133768]

Krauss, G. Intracellular signal transduction: the protein cascades of the MAP kinase pathways. In: Krauss, G., editor. Biochemistry of signal transduction and regulation. 2. WILEY-VCH Verlag Gm BH & Co; Wheinheim: 2001. p. 350

Kücükakin B, Gögenur I, Reiter RJ, Rosenberg J. Oxidative stress in relation to surgery: is there a role for the antioxidant melatonin? J Surg Res. 2009; 152:338–347. [PubMed: 18262562]

Kuhn DM, Geddes TJ. Molecular footprints of neurotoxic amphetamine action. Ann N Y Acad Sci. 2000; 914:92–103. [PubMed: 11085312]

Kumar A, Newberg A, Alavi A, Berlin J, Smith R, Reivich M. Regional cerebral glucose metabolism in late-life depression and Alzheimer disease: a preliminary positron emission tomography study. Proc Natl Acad Sci U S A. 1993; 90:7019–7023. [PubMed: 8346211]

Kunkin J, Peel AL, Mao XO, Xie L, Cottrell BA, Henshall DC, Greenberg DA. Increased hippocampal neurogenesis in Alzheimer's disease. Proc Natl Acad Sci U S A. 2004; 101:343–347. [PubMed: 14660786]

Landfield PW. The role of glucocorticoids in brain aging and Alzheimer's disease: an integrative physiological hypothesis. Exp Gerontol. 1994; 29:3–11. [PubMed: 8187839]

Landfield PW, Linch G. Hippocampal aging and adrenocorticoids; quantitative correlations. Science. 1978; 202:1098–1102. [PubMed: 715460]

Lawrence MS, Sapolsky RM. Glucocorticoids accelerate ATP loss following metabolic insults in cultured hippocampal neurons. Brain Res. 1994; 646:303–306. [PubMed: 8069678]

Le DA, Lipton SA. Potential and current use of N-methyl-D-aspartate (NMDA) receptor antagonists in diseases of aging. Drug Aging. 2001; 18:717–724.

Lenox RH, Hahn C-G. Overview of the mechanism of action of lithium in the brain: fifty-year update. J Clin Psychiatry. 2000; 61(suppl 9):5–15. [PubMed: 10826655]

li H-L, Wang H-H, Liu S-J, Deng Y-Q, Zhang Y-J, Tian Q, Wang X-C, Chen X-Q, Yang Y, Zhang J-Y, Wang C, Xu H, Liao F-F, Wang J-Z. Phosphorylation of tau antagonizes apoptosis by

stabilizing β-catenin, a mechanism involved in Alzheimer's neurodegeneration. Proc Natl Acad Sci U S A. 2007; 104:3591–3596. [PubMed: 17360687]

Linholm D, et al. Activity-dependent and hormonal regulation of neurotrophin mRNA levels in the brain-implications for neuronal plasticity. J Neurobiol. 1994; 25:1362–1372. [PubMed: 7852991]

Littleljohn, D.; Mangano, E.; Hayley, S. Common pathways to neurodegeneration and co-morbid depression. In: Ritsner, MS., editor. Brain protection in schizophrenia, mood and cognitive disorders. Springer; Amsterdam: 2010. p. 185-242.

Liu, J.; Ames, BN. Mitochondrial nutrients: reducing mitochondrial decay to delay or treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease. In: Luo, Y.; Packer, L., editors. Oxidative stress and age-related neurodegeneration. Taylor & Francis Group; Boca Raton, FL: 2006. p. 59-106.

Liu J, Wang X, Shigenaga MK, Yeo HC, Mori A, Ames BN. Immobilization stress causes oxidative damage to lipid, protein, and DNA in the brain of rats. FASEB J. 1996; 10:1532–1538. [PubMed: 8940299]

Liu RY, Unmehopa UA, Zhou JN, Swaab DF. Glucocorticoids suppress vasopressin gene expression in human supra-chiasmatic nucleus. J Steroid Biochem Mol Biol. 2006; 98:248–253. [PubMed: 16483767]

Liu RY, Zhou JN, Hoogendijk WJ, van Heerikhuize J, Kamphorst W, Unmehopa UA, Hofman MA, Swab DF. Decreased vasopressin gene expression in the biological clock of Alzheimer disease patients with and without depression. J Neuropathol Exp Neurol. 2000; 59:314–322. [PubMed: 10759187]

Liu Z, Zhu F, Wang G, Xiao Z, Wang H, Tang J, Wang X, Qiu D, Liu W, Cao Z, Li W. Association of corticotropin-releasing hormone receptor-1 gene SNP and haplotype with major depression. Neurosci Lett. 2006; 404:358–362. [PubMed: 16815632]

Lloyd RV. Mechanism of the manganese-catalyzed auto-oxidation of dopamine. Chem Res Toxicol. 1995; 8:111–116. [PubMed: 7703354]

Luo Y, Hattori A, Munoz J, Qin ZH, Roth GS. Intra-striatal dopamine injection induces apoptosis through oxidation-involved activation of transcription factors AP-1 and NF-kappa B in rats. Mol Pharmacol. 1999; 56:254–264. [PubMed: 10419543]

Lupien SJ, et al. Basal cortisol levels and cognitive deficits in human aging. J Neurosci. 1994; 14:2893–2903. [PubMed: 8182446]

Lupien SJ, et al. Longitudinal study of basal cortisol levels in healthy elderly subjects; evidence for sub-groups. Neurobiol Aging. 1995; 17:95–105. [PubMed: 8786810]

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NPV, Thakur M, McEewen BS, Hauger RL, Meaney MJ. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci. 1990; 1:69–73. [PubMed: 10195112]

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NPV, Thakur M, McEwen BS, Hauger RL, Meaney MJ. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci. 1998; 1:69–73. [PubMed: 10195112]

Lupien SJ, McEwen BS. The acute effects of corticosteroids on cognition: integration of animal and human model studies. Brain Res Rev. 1997; 24:1–27. [PubMed: 9233540]

Macdonald J, Galley HF, Webster NR. Oxidative stress and gene expression in sepsis. Br J Anaesth. 2003; 90:221–232. [PubMed: 12538380]

Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro) inflammatory and oxidative & nitrosative stress pathways. Neuro Endocrinol Lett. 2011; 32:7–24. [PubMed: 21407167]

Maes M, Lin A-h, Delmeire L, Gastel AV, Kenis G, De Jongh R, Bosmans E. Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in post-traumatic stress disorder following accidental man-made traumatic events. Biol Psychiatry. 1999; 45:833–839. [PubMed: 10202570]

Maes M, Yirmyia R, Noraberg J, Brene S, Hibbeln J, Perini G, Kubera M, Bob P, Lerer B, Maj M. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab Brain Dis. 2009; 24:27–53. [PubMed: 19085093]

Magarinos AM, Berdugo JM, McEwen BS. Chronic stress alters synaptic terminal structure in hippocampus. Proc Natl Acad Sci U S A. 1997; 94:14002–14008. [PubMed: 9391142]

Magarinos AM, Garcia Verdugo JM, McEwen BS. Chronic stress alters synaptic terminal structure in hippocampus. Proc Natl Acad Sci U S A. 1997; 94:14002–14008. [PubMed: 9391142]

Mahler P, Davis JB. The role of monoamine metabolism in oxidative glutamate toxicity. J Neurosci. 16:6934–6401.

Mangi HK, Moore GG, Chen G. Clinical and pre-clinical evidence for the neurotrophic effects of mood stabilizers: implications of the pathophysiology and treatment of manic-depressive diseases. Biol Psychiatry. 2000; 48:740–754. [PubMed: 11063971]

Manji HK, Moore GJ, Chen G. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? Biol Psychiatry. 1999; 46:929–940. [PubMed: 10509176]

Manji HK, Moore GJ, Chen G. Lithium up-regulates the cytoprotective protein Bcl-2 in the CNS in vivo: a role for neurotrophic and neuroprotective effects in manic depressive illness. J Clin Psychiatry. 2000; 61:82–96. [PubMed: 10826666]

Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. Nat Neurosci. 2007; 10:609–615.

Matrone C, Ciotti MT, Mercanti CD, Marolda R, Calissano P. NGF (Nerve Growth Factor) and BDNF signaling control amyloidogenic route and Aβ production in hippocampal neurons. Proc Natl Acad Sci U S A. 2008; 105:13139–13144. [PubMed: 18728191]

Mayberg HS, Lewis PJ, Regenold W, Wagner HNJ. Paralimbic hypoperfusion in unipolar depression. J Nucl Med. 1994; 35:929–934. [PubMed: 8195877]

Mazurek MF, Growdon JH, Beal MF, Martin JB. CSF vasopressin concentration is reduced in Alzheimer's disease. Neurol. 1986; 36:1133–1137.

Mazzulli, JR.; Lind, S.; Ischiropoulos, H. Reactive oxygen and nitrogen species: weapons of neuronal destruction. In: Luo, Y.; Packer, L., editors. Oxidative stress and age-related neurodegeneration. Taylor & Francis Group; Boca Raton, FL: 2006. p. 107-120.

McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci. 1999; 22:105–122. [PubMed: 10202533]

McEwen BS, Magarinos AM. Stress and hippocampal plasticity: implications for the pathophysiology of affective disorders. Hum Psychopharmacol. 2001; 16:S7–S19. [PubMed: 12404531]

McIntosh LJ, Hong KE, Sapolsky RM. High glucocorticoid levels decrease some antioxidant enzyme activities in the adult rat brain. Soc Neurosci Abstr. 1995; 21:2129.

Meynen G, Unmehopa UA, Hofman MA, Swaab DF, Hoogendijk WJ. Hypothalamic oxytocin mRNA expression and melancholic depression. Mol Psychiatry. 2007; 12:118–119. [PubMed: 17252002]

Milne, GL.; Gao, L.; Brooks, JD.; Morrow, JD. The role of oxidative stress in diseases associated with overweight and obesity. In: Packer, L.; Sies, H., editors. Oxidative stress and inflammatory mechanisms in obesity, diabetes, and the metabolic syndrome. Taylor & Francis Group; Boca Raton: 2008. p. 33-36.

Mlynarik M, Zelena D, Bagdy G, Makara GB, Jezova D. Signs of attenuated depression-like behavior in vasopressin deficient Brattleboro rats. Horm Behav. 2007; 51:395–405. [PubMed: 17258216]

Moore GH, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. The Lancet. 2000; 356:1241–1242.

Moreira, PI.; Nunomura, A.; Honda, K.; Aliev, G.; Casadeus, G.; Zhu, X.; Smith, MA.; Perry, G. The key role of oxidative stress in Alzheimer's disease. In: Qureshi, GA.; Parvez, SH., editors. Oxidative stress and neurodegenerative disorders. Elsevier; Amsterdam, Boston: 2007. p. 267-282.

Moreira, PI.; Zhu, X.; Nunomura, A.; Smith, MA.; Perry, J. Antioxidant therapies in the prevention and treatment of Alzheimer disease. In: Luo, Y.; Packer, L., editors. Oxidative stress and age-related neurodegeneration. Taylor & Francis Group; Boca Raton, FL: 2006. p. 131-146.

Mory E, Danysz W, Quack G. Potential antidepressant properties of amantadine, memantine and bifemelane. Pharmacol Toxicol. 1993; 72:394–397. [PubMed: 8361950]

Murphy TH, Miyamoto M, Sastre A, Schnaar RL, Coyle JT. Glutamate toxicity in a neuronal cell line involves inhibition of cysteine transport leading to oxidative stress. Neuron. 1989; 2:1547–1558. [PubMed: 2576375]

Murray, RK. Red & white blood cells. In: Murray, RK.; Granner, DK.; Mayes, PA.; Rodwell, VW., editors. Harper's illustrated biochemistry. Lange Medical Books/McGraw-Hill; New York: 2003. p. 611-613.

Myint A-M, Kim Y-K. Cytokine-serotonin interactions through indoleamine-2, 3-dioxygenase: a neurodegenerative hypothesis of depression. Med Hypo. 2003; 61:519–525.

Naoi, M.; Maruyama, W.; Shamoto-Nagai, M.; Kato, Y.; Tanaka, M. Oxidative stress in mitochondria: the involvement in neurodegenerative diseases. In: Packer, L.; Surh, Y-J., editors. Oxidative stress, inflammation and health. Taylor and Francis Group; Boca Raton, London: 2005. p. 423-444.

Nitsch R, Frotscher M. Reduction of posttraumatic trans-neuronal "early gene" activation and dendritic atrophy by the N-methyl-D-aspartate receptor antagonist MK-801. Proc Natl Acad Sci U S A. 1992; 89:5197–5200. [PubMed: 1534412]

Noble W, Planel E, Zehr C, Olm V, Meyerson J, Suleman F, Gay K, Wang L, LaFrancois J, Feinstein B, Burns M, Krishnamurthy P, Wen Y, Bhat R, Lewis J, Dickson D, Duff K. Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. Proc Natl Acad Sci U S A. 2005; 102:6990–6995. [PubMed: 15867159]

Nunomura A, Perry G, Aliev G, et al. Oxidative damage is the earliest event in Alzheimer's disease. J Neuropathol Exp Neurol. 2001; 60:759–767. [PubMed: 11487050]

Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen RB, Smith MA. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol. 2001; 60:759–767. [PubMed: 11487050]

O'Brien JT, Ames D, Schweitzer I, Colman P, Desmond P, Tress B. Clinical and magnetic resonance imaging correlates of hypothalamic-pituitary-adrenal axis function in depression and Alzheimer's disease. Br J Psychiatry. 1996; 168:679–687. [PubMed: 8773809]

Oka A, Belliveau MJ, Rosenberg PA, Volpe JJ. Vulnerability of oligodendroglia to glutamate: pharmacology, mechanisms and prevention. J Neurosci. 1993; 13:1441–1453. [PubMed: 8096541]

Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease. Arch Gen Psychiatry. 2006; 63:530–538. [PubMed: 16651510]

Parker G. Classifying depression? Should paradigms lost be regained? Am J Psychiatry. 2000; 157:1195–1203. [PubMed: 10910777]

Patapoutian A, Reichardt LF. Trk receptors: mediators of neurotrophin action. Cur Opin Neurobiol. 2001; 11:272–280.

Paul IA, Skolnick P. Glutamate and depression: clinical and pre-clinical studies. Ann N Y Acad Sci. 2003; 1003:250–271. [PubMed: 14684451]

Pedrosa R, Soares-da-Silva P. Oxidative and non-oxidative mechanisms of neuronal cell death and apoptosis by L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine. Braz J Pharmacol. 2002; 137:1305–1313.

Perry G, Cash AD, Srinivas R, Smith MA. Metals and oxidative homeostasis in Alzheimer's disease. Drug Dev Res. 2002; 56:293–299.

Perry G, Nunomura A, Raina AK, Smith MA. Aβ junkies. The Lancet. 2000; 355:757.

Perry G, Raina AK, Nunomura A, et al. How important is oxidative damage? Lessons from Alzheimer's disease. Free Radic Biol Med. 2000; 28:831–834. [PubMed: 10754280]

Peters EJ, Slager SL, McGrath PJ, Knowles JA, Hamilton SP. Investigation of serotonin-related genes in antidepressant responses. Mol Psychiatry. 2004; 9:879–889. [PubMed: 15052272]

Plotsky PM. Pathways to the secretion of adrenocorticotropin: a view from the portal. J Neuroendocrinol. 1991; 3:1–9. [PubMed: 19215439]

Pomara N, Sidtis J. Does cortical thinning in persons at increased risk for major depression also increase their risk for Alzheimer's disease? Proc Natl Acad Sci U S A. 2009; 106:E82. [PubMed: 19581594]

Pomara N, Stanley M, Rhiew HB, Bagne CA, Deptula D, Galloway MP, Tanimoto K, Verebey K, Tamminga CA. Loss of the cortisol response to naltrexone in Alzheimer's disease. Biol Psychiatry. 1988; 23:726–733. [PubMed: 3285899]

Porter NM, Landsfield PW. Stress hormones and brain aging; adding injury to insult? Nat Neurosci. 1998; 1:3–4. [PubMed: 10195096]

Radley JJ, Sawchenko PE. A common substrate for prefrontal and hippocampal inhibition of the neuroendocrine stress response. J Neurosci. 2011; 31:9683–9695. [PubMed: 21715634]

Raison, CL.; Purselle, DC.; Capuron, L.; Miller, AH. Treatment of depression in medical illness. In: Licinio, J.; Wong, M-L., editors. Biology of depression: from novel insights to therapeutic strategies. WILEY-VCH Verlag; Weinheim: 2005. p. 253-278.

Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry. 2000; 48:766–777. [PubMed: 11063973]

Rasmuson A, Nasman V, Carlstrom K, Olsson T. Increased levels of adrenocortical and gonadal hormones in mild to moderate Alzheimer's disease. Dement Geriatr Cogn Disord. 2002; 13:74–79. [PubMed: 11844888]

Reisberg B, Doody R, Stöffler A, Schnutt F, Ferris S, Möbius H. Memantine in moderate to severe Alzheimer's disease. N Engl J Med. 2003; 348:1333–1342. [PubMed: 12672860]

Roca CA, Schmidt PJ, Deuster PA, Danaceau MA, Altemus M, Petnam K, Chrousos GP, Nieman LK, Rubinow DR. Sex-related differences in stimulated hypothalamic-pituitary-adrenal axis during induced gonadal suppression. J Clin Endocrinol and Metab. 2005; 90:4224–4231. [PubMed: 15886244]

Rodrigues, R.; Bonda, DJ.; Perry, G.; Castellani, RJ.; Casadesus, G.; Lee, H-g; Lee, H-P.; Wang, X.; Zhu, X.; Petersen, RB.; Smith, MA. Oxidative stress and neurodegeneration: an inevitable consequence of aging: implications for therapy. In: Ritsner, MS., editor. Brain protection in schizophrenia, mood and cognitive disorders. Springer; 2010. p. 305-325.

Rogóz Z, Skuza G, Maj J, Danysz W. Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. Neuropharmacology. 2002; 42:1024–1030. [PubMed: 12128003]

Roy BN, Reid RL, Van Vugt DA. The effects of estrogen and progesterone on corticotropin-releasing hormone and arginine vasopressin messenger ribonucleic acid levels in the paraventricular nucleus and supraoptic nucleus of the rhesus monkey. Endocrinology. 1999; 140:2191–2198. [PubMed: 10218971]

Sapolski MS. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry. 2000; 48:766–777. [PubMed: 11063973]

Sapolski MS. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry. 2000; 48:766–777. [PubMed: 11063973]

Sapolsky RM. Depression, antidepressants, and the shrinking hippocampus. Proc Natl Acad Sci U S A. 2001; 98:12320–12322. [PubMed: 11675480]

Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure. J Neurosci. 1990; 10:2897–2902. [PubMed: 2398367]

Scolville, WBl; Milner, B. Hippocampal damage and memory dysfunction. J Neurol Psychiatry. 1957; 20:11–21.

Segal RA. Selectivity in neurotrophin signaling: theme and variations. Annu Rev Neurosci. 2003; 26:299–330. [PubMed: 12598680]

Shanmugham, B.; Alexopoulus, G. Geriatric depression. In: Licinio, H.; Wong, M-L., editors. Biology of depression: from novel insights to therapeutic strategies. Willey-VCH Verlag GmbH & Co; Weinheim: 2005. p. 319-340.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A. 1996; 93:3908–3913. [PubMed: 8632988]

Shorter, E.; Fink, M. Cortisol. In: Shorter, E.; Fink, M., editors. Endocrine psychiatry: solving the riddle of melancholia. Oxford University Press; London: 2010. p. 31-50.

Smith MA, Drew KL, Nunomura A, Takeda A, Hirai K, Zhu X, Atwood CS, Raina AK, Rottkamp CA, Sayre LM, Friedland RP, Perry G. Amyloid-β, tau alterations and mitochondrial dysfunction

in Alzheimer disease: The chickens or the eggs? Neurochem Int. 2002; 40:527–531. [PubMed: 11850109]

Snyder SH. Serotonin, cytokines, p11, and depression. Proc Natl Acad Sci U S A. 2011; 108:8923–8924. [PubMed: 21593414]

Sopolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocrinol Rev. 1986; 7:284–301.

Sotiropoulos I, Catania C, Pinto LG, Silvia R, Pollerber GE, Takashima A, Sousa N, Almeida OFX. Stress acts cumulatively to precipitate Alzheimer's disease-like tau pathology and cognitive deficits. J Neurosci. 2011; 21:7840–7847. [PubMed: 21613497]

Sprague JE, Everman SL, Nichols DE. An integrated hypothesis for the serotonergic axonal loss induced by 3, 4-methylenedioxymethamphetamine. Neurotoxicology. 1998; 19:427–441. [PubMed: 9621349]

Starkstein SE, Jorge R, Mizrahi R, Robinson RG. The construct of minor and major depression in Alzheimer's disease. Am J Psychiatry. 2005; 162:2086–2093. [PubMed: 16263848]

Stokes, KY.; Tailor, A.; Granger, DN. Role of oxidative stress in hypercholesterolemia-Induced inflammation. In: Surh, Y-J.; Packer, L., editors. Oxidative stress, inflammation and health. Taylor and Francis Group; Boca Raton: 2005. p. 221-244.

Swaab DA, Bao A-M. (Re-) activation of neurons in aging and dementia: lessons from the hypothalamus. Exp Gerontol. 2011; 46:178–184. [PubMed: 20833237]

Swaab DF, Gao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. Res Rev. 2005; 4:141–194.

Terracciano A, Lobina M, Peras MG, Mulas A, Cannas A, Meirelles O, Sutin AR, Zonderman AB, Uda M, Crisponi L, Schlessinger D. Neuroticism, depressive symptoms, and serum BDNF. Psychosom Med. 2011; 73:638–642. [PubMed: 21949427]

Thomas AJ, Morris C, Davis S, Jackson E, Harrison R, O'brien JT. Soluble cell adhesion molecules in late-life depression. Int Psychogeriatr. 2007; 4:1–7.

Toro, G.; Rodrigo, R. Oxidative stress, basic overview. In: Rodrigo, R., editor. Oxidative stress and antioxidants: their role in human disease. Nova Science Publishers Inc; New York: 2009. p. 1-24.

Vallone D, Picetti R, Borrelli E. Structure and function of dopamine receptors. Neurosci Biobehav Rev. 2000; 24:125–132. [PubMed: 10654668]

Vincent SL, Todtenkopf MS, Benes FM. A comparison of the density of pyramidal and not pyramidal neurons in the anterior cingulate cortex of schizophrenics and manic- depressives. Soc Neurosci. 1997; 23:2199.

Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ, Greengard P. Antidepressant effects of selective serotonin reuptake inhibitors (SSRI) are attenuated by anti-inflammatory drugs in mice and humans. Proc Natl Acad Sci U S A. 2011; 108:9262–9267. [PubMed: 21518864]

Weingarten P, Bermak J, Zhou QY. Evidence for non-oxidative dopamine cytotoxicity: potent activation of NF-kappa B and lack of protection by anti-oxidants. J Neurochem. 2001; 76:1794–1804. [PubMed: 11259497]

Wilson RS, Barnes LL, Mendes de Leon CF, Aggarwal NT, Schneider JA, Bach J, Pilat J, Beckett LA, Arnold SE, Evans DA, Bennett DA. Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurol. 2002; 59:364–370.

Woo NH, Teng HK, Siao C-J, Chiaruttini C, Pang PT, Milner TA, Hempstead BL, Lu B. Activation of p75NTR by pro-BDNF facilitates hippocampal long-term depression. Nat Neurosci. 2005; 8:1069–1077. [PubMed: 16025106]

Wooleley CS, Weiland NG, McEwen BS, Schwartzkroin PA. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. J Neurosci. 1997; 17:1848–1859. [PubMed: 9030643]

Woolley CS, Gould E, Sakay R, Spencer R, McEwen BS. Effects of aldosterone or RU2862 treatment on adrenalectomy-induced cell death in the dentate gyrus of the adult rat. Brain Res. 1998; 554:312–315. [PubMed: 1933312]

Woolley CS, Gould E, Frankfurt M, McEwen CS. Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. J Neurosci. 1990; 10:4035–4039. [PubMed: 2269895]

Wright SL, Persad C. Distinguishing between depression and dementia in older persons: neuropsychological and neuropathological correlates. J Geriatr Psychiatry Neurol. 2007; 20:189–198. [PubMed: 18004006]

Wurster, AL.; Grusby, MJ. Cytokines. In: Lennarz, WJ.; Lane, MD., editors. Encyclopedia of biological chemistry. Elsevier Inc; 2004. p. 550-555.

Zaudig, M. The prodromes and early detection of Alzheimer's disease. In: Maj, M.; Lopez-Ibor, JJ.; Sartorius, N.; Sato, M.; Okasha, A., editors. Early detection and management of mental disorders. John Wiley & Sons Ltd; England: 2005. p. 277-294.

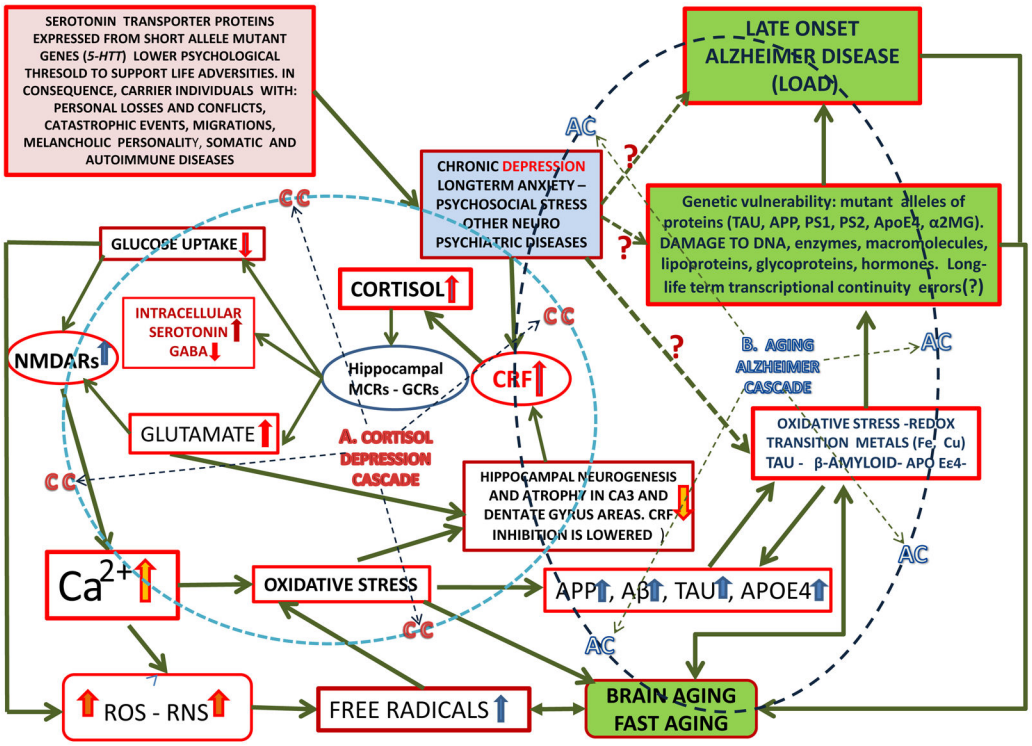

Fig. 1.

Proposed molecular interaction between two neuropathologies such as major depressive disorder and Alzheimer's disease. It is impossible to avoid complexity, by reason of the many genotypes and phenotypes involved. Two molecular "cascades" are sketched and greatly simplified, as many more enzymes, proteins, transcription factors, genome changes, to name a few, are involved, opening new fields of research and therapeutic applications.

A. Cortisol Depression Cascade. The currently established genome of more than 40% of chronic, long-standing, depressed-anxious-stressed patients – which are short mutant alleles of the serotonin transporter protein genes (*5-HTT*) carriers – induces a vulnerability to the personality threshold to withstand normal and severe life adversities and diseases. Significantly, in more (40–50%) carriers of *5-HTT* short alleles than not, they develop depressive major crises or chronic dysthymia with long term, severe anxiety and stress. Chronic depression elevates corticotrophin release factor, activating the hypothalamus-pituitary-adrenal axis and increasing cortisol levels significantly, particularly in hippocampal areas with glycocorticoid and mineralocorticoid receptors. Neurotransmitters are led to dyshomeostasis and glucose uptake falls in hippocampal neurons. Glutamate receptors (NMDARs) in particular are robustly activated, and intracellular Calcium elevated. These two factors contribute to oxidative stress and, directly, to inhibition of hippocampal neurogenesis and atrophy, impairing its inhibition of CRF and elevating its levels, closing the cycle.

B. The "Aging Alzheimer Cascade" progresses during late life, influencing and influenced by free radicals – reactive oxygen species (ROS) and reactive nitrogen species (RNS), oxidative stress, redox transition metals – iron (Fe) and copper (Cu), and increased deposition of amyloid-β peptide (Aβ) as a consequence of increased levels of amyloid-β

protein precursor (AβPP); and of Tau and Apolipoprotein Eε4 (ApoEε4). During aging, two main factors may contribute to close the cycle: 1 - accumulation of free radicals-oxidative stress with damage to proteins, fatty acids, glycoproteins, DNA; and 2 - genetic vulnerability: mutant alleles in specific genes leading to dysfunction of the many complex – defense and pathological - roles of the key proteins in AD: AβPP, Aβ, Tau, ApoE4; possible accumulation, with long-term life repetitions, of “transcriptional continuity errors”, and other unknown factors. Finally, the advent of Alzheimer’s disease closes the cycle, since it means fast brain aging. The figure does not indicate whether AD is the normal final pathway--a closed system with no entries or deaths, at 100 years of age, persons without AD are the absolute minority (17–20%); and AD individuals are the majority (70–80%) (Rodrigues et al. 2010).

This Figure, which exhibits the various interactions of both cascades, raises the question of whether these pathologies are analogous or very close biological processes which occur sequentially during the life cycles.

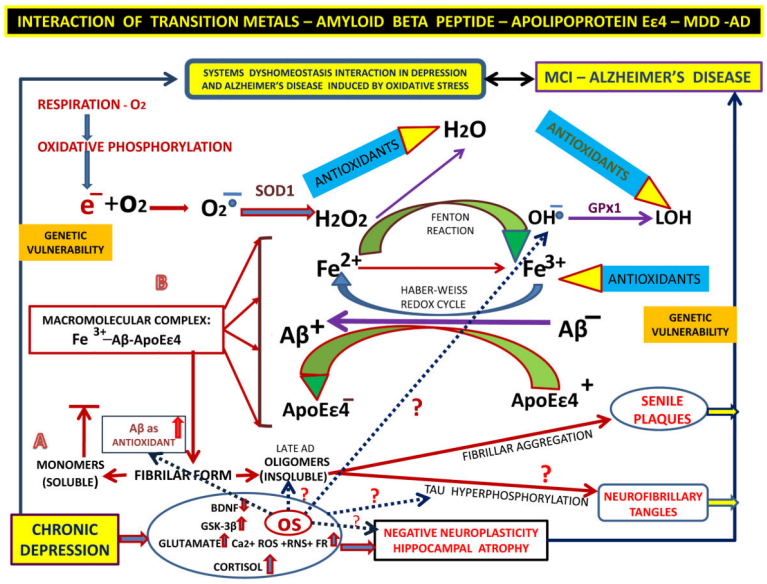

Fig. 2.

An example of how chronic depression might interact with metal redox systems and antioxidant defenses of the Fenton reaction and Haber-Weiss metal cycle, which can lead to mild cognitive impairment (MCI) and Alzheimer's disease (AD), if oxidative stress and genetic vulnerability to neurodegeneration cannot be efficiently controlled.

A. Chronic depression is associated with cortisol increased levels which, through the "cortisol cascade" (see fig. 1) in hippocampus, leads to dyshomeostasis of the neurotransmitter systems, particularly glutamate elevation and consequent Calcium intracellular increased concentration. The key interaction process between AD and MDD is oxidative stress originated from neurotoxicity, once Calcium elevated levels generate ROS (reactive oxygen species) and RNS (reactive nitrogen species); and free radicals. By its turn, depression generated OS interacts with aging and AD, phenotypes known to be OS induced (not shown in the sketch). By four ways this interaction might occur: inducing Aβ elevation as antioxidant defense; increasing strong free radicals such as OH· and others; contributing to Aβ oligomer formation; and through hippocampal atrophy in brain regions where AD shows atrophy. In the figure, some factors that may be intermediary between both illnesses are shown as examples (many other molecular processes exist that are not shown here): glycogen synthase kinase-3β (GSK-3β) increases its intracellular level and activates TAU hyperphosphorylation contributing to neurofibrillary tangles (NFTs) formation. Brain derived neurotrophic factor (BDNF) levels decline as a result of the "cortisol cascade"; BDNF levels also decline in AD. In both cases survival functions and nuclear synthesis counter neural apoptosis and other neurodegenerative processes are impaired with drop in BDNF.

B. We illustrate how oxidative phosphorylation creates free radicals (OH· hydroxyl radical for example) and how antioxidants usually control homeostasis (SOD1, superoxide dismutase; GPx1, glutathione peroxidase) avoiding oxidative stress (transforming free radicals in water, H_2O, or lipid alcohols, LOH). However, with genetic vulnerability – as in cases of mutant alleles of the proteins APP (amyloid precursor protein), PS1, PS2 (pre-senilins 1 and 2), τ (tau), and ApoEs (apolipoproteins E) whose functions are currently

thought to normally protect against oxidative stress and neurodegenerative processes – redox transition metals such as Fe and Cu may not be efficiently controlled because the binding on macromolecular complexes – ApoEε4, Aβ and Fe - in higher neural levels than normally. These complexes might be excessively created and lead to insoluble Aβ oligomers (instead of soluble Aβ monomers) which turn on amyloid deposits. Genetic vulnerability in chronic depression that reinforces MCI, AD or other neurodegenerative illnesses has been shown in Fig. 1.

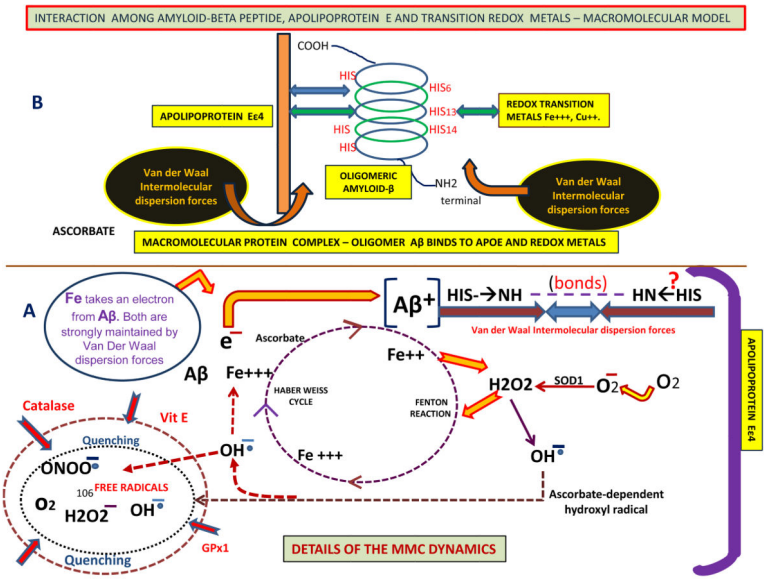

Fig. 3.

Illustration of how macromolecular complexes ApoEε4-Aβ oligomers-redox transition metals might be maintained in bound state; and the molecular dynamics which may sustain them in Aβ monomer solution or, in case of excessive β-Amyloid peptide formation and ApoEε4 disproportionate interference, in Aβ insoluble oligomers.

A – A model of the macromolecular complex dynamics is presented. Fe+++ is bound to Aβ as it takes an electron from it, turning on Aβ+. By the Fenton reaction Fe++ then generates the strong hydroxyl radical. This and other free radicals are buffered by antioxidants GPx1, catalase, Ascorbate, Vit E and others. Using antioxidants Fe++, through the Haber-Weiss cycle, regenerates Fe+++, maintaining its binding to Aβ+. In its turn, ApoEε4 may be bound to Aβ+ through histidine NH bonds. Van der Waal intermolecular dispersion forces impair aggregation of Aβ peptide and it stays free as soluble monomers.

B - If there is impairment of MMC dynamic homeostasis, particularly when Aβ peptide increases excessively by oxidative stress, genetic vulnerability, or there is overload of ApoEε4 or redox transition metals (RTMs) bias impairing Fe dynamic function, then histidine NH bonds get stronger bonds which cannot be separated by Van der Waal forces. The result may be aggregation and deposition of the insoluble oligomers formed.

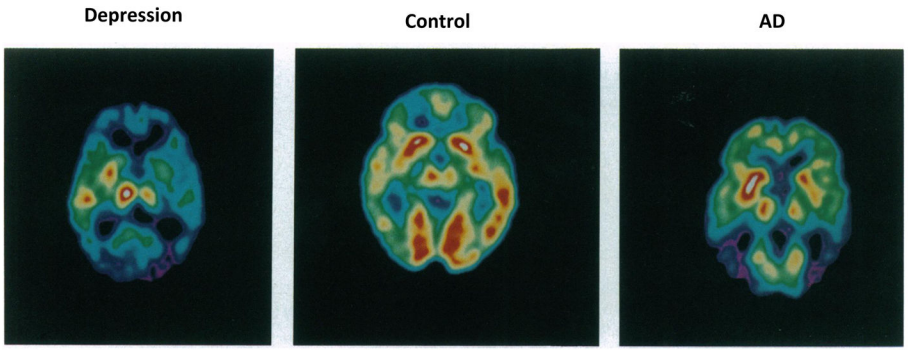

Fig. 4.

18 FDG (fluorodeoxyglucose) uptake in the cortical and subcortical regions at the level of the basal ganglia in late-life depression, DAT, and an age-matched control. Orange and red show areas of high FDG uptake; green and blue represent regions with low FDG uptake. The right side of the image represents the left side of the brain and vice versa. Note the widespread decline in FDG uptake that occurs in late-life depression and DAT relative to the control.