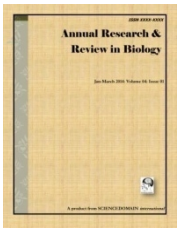

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Mechanisms of Prooxidants in NeuroInflammatory Processes and Clinical Manifestations

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Authors' contributions

This work was carried out in collaboration between all authors. Authors CGD and JOH coordinated information and wrote manuscript. Authors HGE and OBN make recompilation of data and compared with information previously published by our lab. Author SGJA reviewed integral content of manuscript and format adopted to the presentation of the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

In clinic practice the reduction of cerebral blood flow in particular zones of the brain as brainstem can cause early cerebral damage then, ischemia and posterior reperfusion induce an inflammatory response leading to further cellular death. Indeed, inflammatory cells may release deleterious compounds or cytokines that exacerbate oxidative damage to metabolically compromised neurons, and similar mechanisms may operate in the pathophysiology of neurodegenerative diseases in which vascular factors, inflammation and oxidative stress are implicated. In the present work, the issue referent to mechanisms of pro-oxidants in inflammatory processes, and its relation with common pathogenesis and clinical manifestations are analyzed in detailed and updated form.

Keywords: Amino acids; calcium; lipid peroxidation; neurotoxicity; pro-oxidants.

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1. INTRODUCTION

Neuroinflammation diseases rise to complications that affect cognitive regions of the cerebrum, modulate the memory, or culminate in neurodegenerative diseases (ND) [1], especially those induced by the presence of free radicals in central nervous system (CNS) [2], that make the cells of this system susceptible to oxidative damage caused by excessive production of reactive oxygen species (ROS) implicated in pathologic process [3]. This review was undertaken to investigate possible protection by the neuroprotective and/or anti-inflammatory drugs that have different putative mechanisms of action, as consequence of neuroinflammation diseases or neurological disorders; due an early neuroprotective effect does not necessarily lead to increased long-term neuronal survival.

Free radicals (FR) are reactive species possessing unpaired electron that principally comes from nitrogen and oxygen metabolism, and are generated from normal metabolic reactions, and exogenous factors can increase them [4]. This group is formed by one superoxide anion, one hydroxyl radical and FR that come from organic compounds: alcoxyl, peroxyl, hydrogen peroxide and singlet oxygen [5] (Fig. 1).

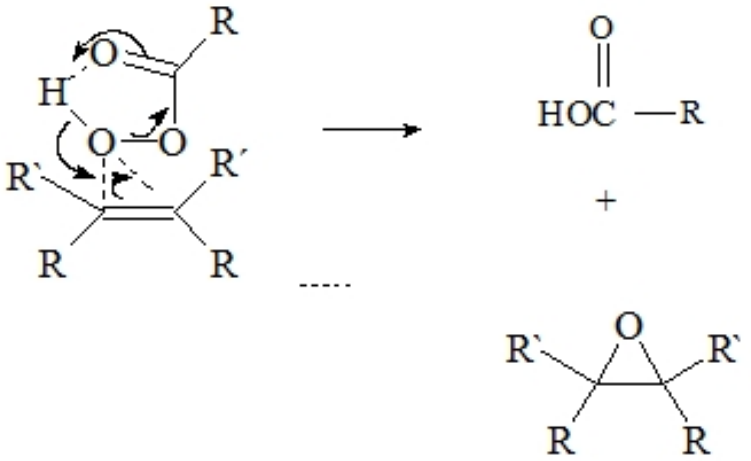

Fig. 1. Formation of superoxide anion, hydroxyl radical and FR that come from organic compounds: alcoxyl, peroxyl, hydrogen peroxide and singlet oxygen.

Therefore, the general denomination ROS is used nodaway to include chemical species that act like oxidants but that are not FR (hydrogen peroxide, hypochlorous acid, hydroperoxides and epoxide metabolites) see Table 1 [6].

These substances have been implicated in oxidative stress mechanism and cerebral dysfunction leading to neurodegenerative disorders related to age [7]. An alternative to combat endogenous free radicals induced by aging and neurodegenerative diseases requires the presence of absorbers of free radicals [8].

Table 1. Main reactive oxygen species

Name	Formula	Formation
Superoxide	0_2-	Intermediate in 0_2 reduction to H_2O
Hydroxyl	HO.	Powerful oxidant in biological systems
Peroxyl	ROO.	Low oxidant ability, but high diffusibility
Alkoxyl	RO.	Medium oxidant ability with lipids
Hydrogen peroxide	H_20_2	Originated from 0_2
Hypochlorous acid	$HClO^-$	Formed through mieloperoxidase action
Singlet oxygen radiation	lO_2	Molecularly excited oxygen through sunlight and

**Adapted from Juárez and Calderón 2009 [6]*

Glutathione (GSH) is the principal regulator of redox equilibrium and contributes to protection of tissues exposed to oxidizing agents, which can damage the cell membrane lipids [9]. The excessive formation of FR could be interpreted as oxidizing damage, which have dual participation not only deleting, but also beneficial effects to maintain the physiological functions of every cell structure [10].

Inflammatory diseases associated with pain are often difficult to treat in the clinic due to insufficient understanding of the nociceptive pathways involved. For example, acute ischemic stroke is a clinical condition accompanied by inflammation and oxidative stress. In patients suffering from this problem, the levels of inflammation markers as high-sensitivity C-reactive protein [hs-CRP], fibrinogen, erythrocyte sedimentation rate, and white blood cell count are high [11].

There has been considerable interest in the role of ROS in inflammatory disease, but still, little is known on the role of hydrogen peroxide (H_2O_2) in hyperalgesia. Keeble et al. [12], demonstrated the notable effect of H_2O_2 in mediating inflammatory hyperalgesia, thereby highlighting H_2O_2 removal as a novel therapeutic target for anti-hyperalgesic drugs in the clinic.

Although the inhalation of highly concentrated solutions of hydrogen peroxide can cause severe irritation and inflammation of mucous membranes, with coughing and dyspnea, the mechanism of damage in the CNS is thought to be by arterial gas embolism with subsequent brain infarction. The rapid generation of oxygen in closed body cavities can also cause mechanical distension, and there is potential for the rupture of the hollow viscous secondary to oxygen liberation [13].

Inflammation is deleterious for organs with reduced capacity of regeneration, such as the brain. In patients who are very sick, supportive treatment, such as mechanical ventilation, is equally important and several drugs are used to reduce brain swelling and inflammation, or simply affect cerebral functions and causes health complications [14].

1.1 Immune Response

Peripheral inflammation leads to immune responses in brain. These responses are characterized by microglial activation, elaboration of pro-inflammatory cytokines and ROS, and secondary neuronal injury. The inducible cyclooxygenase (COX), COX-2, mediates a significant component of these responses in brain Via downstream pro-inflammatory PG signaling [15]. Shi et al. reported that PGE2 EP4 signaling mediates an anti-inflammatory effect in brain by blocking LPS-induced proinflammatory gene expression in mice, and

suggested that EP4 selective agonist decreased LPS-induced proinflammatory gene expression in hippocampus and in isolated adult microglia. In plasma, EP4 agonist significantly reduced levels of pro-inflammatory cytokines and chemokines, indicating that peripheral EP4 activation protects the brain from systemic inflammation.

Beside, Ullen et al. [16] propose that one of the oxidants released by activated leukocytes is hypochlorous acid (HOCl) formed via the myeloperoxidase (MPO)-H2O2-Cl(-) system, which evidence that interference with the MPO pathway could protect against BBB dysfunction under (neuro) inflammatory conditions.

Reports about treatment options have been developed for clinical management of the complications of clinical disorders (Table 2). Those studies suggest relevant substances to ameliorate oxidative stress and can prevent or retard the development of have involved oxidative stress and antioxidant agents could prove to be useful for treating patients with those disorders, because patients with a severe trauma exhibit a strong oxidative stress, an intense inflammatory response, and long-lasting hypermetabolism, all of which are proportional to the severity of injury [17].

1.2 Role of Pro-oxidants in Inflammatory and Neurodegenerative Diseases

Pro-oxidants are chemicals that induce oxidative stress, either by generating ROS or by inhibiting antioxidant systems [33]. The oxidative stress produced by these chemicals can damage cells and tissues, for example an overdose of the analgesic paracetamol (acetaminophen) can fatally damage the liver, partly through the production of ROS [34,35]. Some substances can serve as either antioxidants or pro-oxidants, depending on conditions [36]. This conditions that are important include the concentration of the chemical and if oxygen or transition metals are present.

1.3 Oxidative Stress

Neurodegenerative diseases as Alzheimer (AD) and Parkinson (PD) are age-related disorders characterized by deposit of abnormal forms of specific proteins in the brain [37]. Fig. 2 shows mechanism of a neurodegenerative disease [38].

A growing body of evidence suggests that the accumulation of misfolded proteins is likely to be a key event in PD neurodegeneration. Pathogenic mutations may directly induce abnormal protein conformations (as believed to be the case with synuclein) or damage the ability of the cellular machinery to detect and degrade misfolded proteins (Parkin, UCH-L1); the role of DJ-1 remains to be identified. Oxidative damage, linked to mitochondrial dysfunction and abnormal dopamine metabolism, may also promote misfolded protein conformations. It remains unclear whether misfolded proteins directly cause toxicity or damage cells via the formation of protein aggregates.

(Lewy body). Controversy exists regarding whether Lewy bodies promote toxicity or protect a cell from harmful effects of misfolded proteins by sequestering them in an insoluble compartment away from cellular elements. Oxidative stress, energy crisis (i.e., ATP depletion) and the activation of the programmed cell death machinery are also believed to be factors that trigger the death of dopaminergic neurons in Parkinson's disease [38].

Table 2. Biomarkers of events and clinical disorders that induce inflammation

Clinical disorders	Biomarkers	Tissue	Reference
Atherosclerosis	Activation of NADPH oxidase	Caveolae	Hayashi et al. [18]
Metabolic síndrome	C-reactive protein	Blood	Pizent et al. [19]
Anemia of inflammation	Pro-inflammatory macrophageal cytokines (IL-6, IL-l alpha), and tumor necrosis factor-alpha	Hepatic cells	Smirnov, [20]
Dialyzed patients	C-reactive protein	Blood	Guo et al. [21]
Atherosclerosis	Plasma high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6.	Human aortic endothelial cells	(Bao et al. 2010) [22]
Sporadic colorectal adenoma	Tumor necrosis factor-alpha (TNF-alpha), interleukin-6	Plasma	Hopkins et al. [23]
Neurological disorders	Cytokines	Blood	Prasad [24]
Severe trauma	Interleukin-6/10, and nuclear factor kappa binding (NF-kappaB) activity.	Serum	Yuan et al. [25]
Chronic inflammation (Diabetes)	Brain angiotensin II (Ang II), monocyte/macrophage (ED-1 positive cells), CD8.	Brain	Vargas et al. [26]
Multiple sclerosis	CD3 positive T cells and human leucocyte antigen-D expressing macrophages and microglia in the lesions.	Oligodendrocytes and astrocytes	(Haider et al. [27]
Cerebral ischemic injury	Inflammatory cytokines TNF-α and IL-6	PC-12 cells	(Rajput et al. [28]
Huntington's disease	Pro-inflammatory cytokines, TNF-α, IL-6	Striatum	(Kalonia and Kumar [29]
Alzheimer´s Disease	Microglia, astrocytes and cytokines	Blood	(Galasko and Montine, [30]
Hypoxia and hyperthermia	TNF-alpha, nitrite/nitrate, and MDA/4-HAD	Brain	(Wang et al. [31]
Alzheimer´s Disease	Activation of glial cells and release of Interleukin-1β (IL-1β) and IL-18	Brain	(Liu and Chan [32]

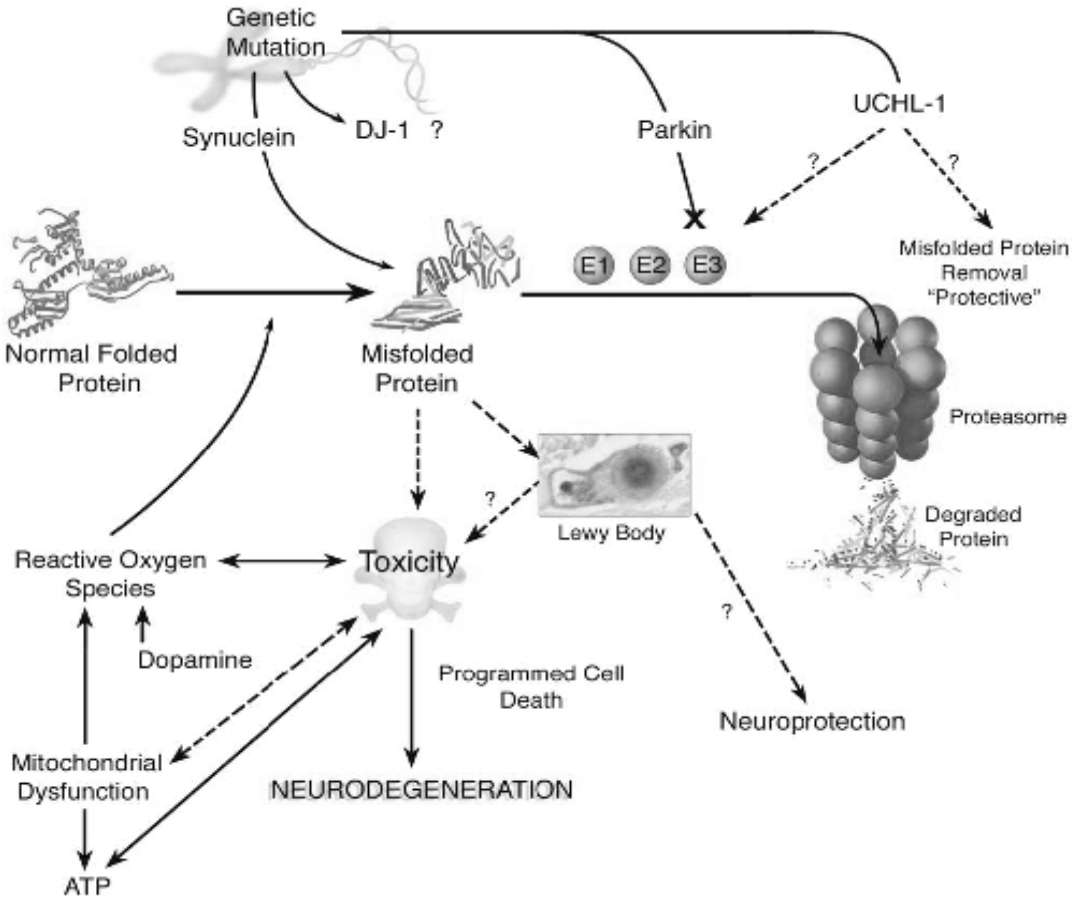

Fig. 2. Mechanisms of Neurodegeneration suggest by Dauer and Przedborski

However, the underlying factor in neurological disorders is increased oxidative stress substantiated by the findings that the protein side-chains are modified either directly by ROS or reactive nitrogen species (RNS), or indirectly by the products of lipid peroxidation [39]. The level of oxidative stress in brain of patients with AD is reflected by an increment in the content of iron (Fe) and copper (Cu), both of which are capable of stimulating free radical formation [40].

Iron is an important catalyst of oxidative radical reactions and promotes the formation of hydroxyl radical from superoxide anion radical and hydrogen peroxide. This means that free iron may directly promote inflammation and that iron chelating agents may have useful anti-inflammatory properties [41].

Inflammatory and neurodegenerative diseases are pathological conditions involving oxidative stress. An important source of ROS are lipoxygenases (LOX) - enzymes responsible for the metabolism of arachidonic acid and other polyunsaturated fatty acids. LOX inhibitors have a protective effect in inflammatory diseases and in neurodegenerative disorders because of its anti-inflammatory activity [42]. Lipid messengers participate in the interactions among neurons, astrocytes, oligodendrocytes, microglia, cells of the microvasculature, and other cells.

A single treatment with acetylcholinesterase (AChE) inhibitors at the beginning of hyperoxia attenuates the detrimental effects of oxygen toxicity in the developing brain. These compounds are currently used for the treatment of AD, as potential candidates for adjunctive neuroprotective therapies to the immature brain. Indeed, the cholinergic anti-inflammatory pathway is a neural mechanism that suppresses the innate inflammatory response and controls inflammation by employing acetylcholine as the key endogenous mediator [43].

Inducible nitric oxide synthase (i.NOS) is the major contributor to the initiation and exacerbation of the central nervous system (CNS) inflammatory/degenerative conditions through the production of excessive NO which generates reactive nitrogen species (RNSs). Activation of iNOS and NO generation have came to be accepted as a marker and therapeutic target in neuroinflammatory conditions such as those observed in ischemia, multiple sclerosis (MS), spinal cord injury (SCI), AD and inherited peroxisomal and lysosomal disorders. iNOS is one of the three NOS isoforms that generates nitric oxide (NO) by converting l-arginine to l-citrulline [44]. NO generated from GSNO acts as second messenger molecule which through S-nitrosylation controls important cellular processes by regulating the expression and the activity of certain proteins such as NF-kappaB.

1.4 Neurodegenerative Disorders

With respect to neurological disorders, if the inflammatory response is persistent it may become chronic. Any chronic inflammatory process can damage healthy tissue and the brain may be particularly vulnerable, since neurons once lost cannot be replaced [45]. There is a significant evidence of the central role of inflammation in the development of AD, a progressive neurodegenerative disorder that destroys the memory and cognition; communicative ability with the social environment; and the ability to carry out daily activities. As astrocytes or microglia activation (reactive gliosis), and associated inflammatory events play a decisive role in the neurodegeneration, they could represent a target for treating these neurodegenerative disorders [46].

Recently, studies have focused on investigating the therapeutic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) in Alzheimer, Parkinson, and Huntington's diseases; and multiple sclerosis. Excitotoxicity is a pathological process which occurs when receptors for the excitatory neurotransmitter glutamate as N-methyl-D-aspartate (NMDA) receptors, are over-activated. D-serine is one of the co-agonist of NMDA receptors, and increased levels of D-serine are associated with excitotoxicity [47]. Kynurenine pathway generates excitotoxic NMDA receptor agonist, quinolinic acid and glutamate antagonist, kynurenic acid, as well as free-radical generators. Therefore, this study suggests that in brain-damaged patients, increased activation of kynurenine pathway, oxidative stress, and raised levels of inflammation continue to take place many years after the original insult [48]. Such abnormalities in kynurenine pathway may play a role in Huntington's disease (HD), a disorder characterized by evidences of persistent inflammation [49].

Table 3. Common drugs used to reduce brain inflammation

Num	Drug	Biomarkers	Reference
1	Colchicine (Cuc)	Neuronal degeneration, cellular apoptosis and iNOS expression	Gahm et al. [54]
2	Fisetin (Com)	Pro-inflammatory cytokines, such as tumor necrosis factor alpha, interleukin-1β.	Prakash et al. [46]
3	Trehalose (Com)	Pro-inflammatory cytokines, and endothelin-1	Echigo et al. [55]
4	Atorvastatin (Cuc)	Anti-inflammatory responses	Piermartiri et al. [56]
5	Ibuprofen (Cuc)	Microglial NADPH oxidase (NOX_2) activation	Wilkinson et al. [57]
6	Zileuton (Cuc)	Reduces lipid peroxidation and inhibit expression of NF-kappaB	Tu el at. [58]
7	Caffeic acid phenethyl ester (Com)	Suppresses about 70% of TNF-alpha, 26% of IFN-gamma and NOS	Celik and Erdogan [59]
8	Rofecoxib, valdecoxib (Cuc)	Non-selective and selective COX-2 inhibitors	Kumari et al. [60]
9	DL-alpha lipoic acid (Com)	Nuclear factor kappa-B (NFkappaB) and glial fibrillary acidic protein (GFAP).	Jesudason et al. [61]
10	Dimemorfan (Cuc)	Inflammation-related signals (p38 mitogen-activated protein kinase, nuclear factor-kappaB, and signal transducer and activator of transcription-1)	Shen et al. [62]
11	Methylene Blue (Cuc)	Decrease of lipid peroxidation and inflammation	Wiklund et al. 2007; Castillo and Leira [63,64]
12	Melatonin (Cuc)	Expression of glial fibrillary acidic protein (GFAP) and nuclear factor kappa B (Nf kappa B)	Jesudason et al. [65]

Commonly used in clinic (Cuc), Used as complement (Com)

Other studies indicate that chronic use of NSAIDs reduces the risk of developing AD in healthy aging populations, because NSAIDs inhibit the enzymatic activity of the inflammatory cyclooxygenases COX-1 and COX-2. The deletion of PGE(2) EP3 receptor in a model of Aβ(42) peptide-induced neuroinflammation reduced proinflammatory gene expression, cytokine production, and oxidative stress. The findings of Shi et al., [50], identified PGE(2) EP3 receptor as a novel proinflammatory, proamyloidogenic, and synaptotoxic signaling pathway, and suggested the role of COX-PGE(2) -EP3 signaling in the development of AD. These findings were in accordance with that of Liang et al., [51], who identified EP2 receptor signaling as a novel proinflammatory and proamyloidogenic pathway, and put up the rationale for developing a therapy that targets EP2 receptor in neuroinflammatory diseases as AD.

Kubera et al. [52], suggested that neurodegeneration and reduced neurogenesis that characterize depression are caused by inflammation. External stress-induced depression-like behaviors are associated with a) increased interleukin-(IL)1β, tumor necrosis factor-α, IL-6, nuclear factor κB, cyclooxygenase-2, expression of Toll-like receptors and lipid peroxidation and b) antineurogenic effects and reduced brain-derived neurotrophic factor (BDNF) levels. Stress-induced inflammation, e.g. increased IL-1β, but not reduced neurogenesis, is sufficient to cause depression. As pharmacological action, antidepressants a) reduce peripheral and central inflammatory pathways by decreasing IL-1β, TNFα, and IL-6 levels; b) stimulate neuronal differentiation, synaptic plasticity, axonal growth, and regeneration through stimulatory effects on the expression of different neurotrophic factors, e.g. trkB, the receptor for brain-derived neurotrophic factor [52]. Indeed, pro-inflammatory cytokines (TNF-alpha and IL-1), secretory phospholipase A2 IIA, and lipoprotein-PLA2 are implicated in vascular inflammation. These inflammatory responses promote atherosclerotic plaques, and formation and release of blood clot that can induce ischemic stroke. TNF-alpha and IL-1 alter lipid metabolism and stimulate production of eicosanoids, ceramide, and ROS that potentiate CNS injuries and certain neurological disorders [53]. Adibhatla and Hatcher suggested that understanding cytokine-induced changes in lipid metabolism will promote novel concepts and steer bench-to-bedside transition for therapies.

Finally, some authors propose that the clinical efficacy of anti-inflammatory substances may be ascribed to their ability to reverse these different pathways (Table 3 above), that could attenuate acute inflammatory responses and brain injury.

2. CONCLUSION

In clinical practice the reduction in cerebral blood flow in a particular cerebral zone as midbrain causes very early cerebral damage as a consequence of a significant liberation of neuroexcitatory amino acids, followed by an excessive entry of calcium into the cells. This process brings about lipid peroxidation, damage of cellular membranes, nuclear destruction, and neuronal death. Moreover, ischemia and posterior reperfusion induce an inflammatory response leading to further cellular destruction. It is to say that therapeutic interventions should aimed at decreasing pro-inflammatory cytokines and cell adhesion molecules i.e. in patients with deteriorating cerebral infarct. Indeed, inflammatory cells may release deleterious compounds or cytokines that exacerbate the oxidative damage to metabolically compromised neurons, and similar mechanisms may operate in the pathophysiology of neurodegenerative diseases in which vascular factors, inflammation and oxidative stress are implicated.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Maiese K, Chong ZZ, Shang YC. Mechanistic insights into diabetes mellitus and oxidative stress. Curr Med Chem. 2007;14:1729-1738.
2. Tang MX, Jacobs D, Stern Y, Marder K. Effect of oestrogen during menopause on risk and age at onset of Alzheimer disease. Lancet. 1996;348:429-432.
3. Coyle JT, Puttfarcken P. Oxidative stress, glutamate and neurodegenerative disorders. Science. 1993;262:689-695.
4. Miller JK, Brzezinska-SIebodzinska E, Madsen FC. Oxidative stress, antioxidants, and animal function. J Dairy Sci. 1993;76:2812-2823.
5. Halliwell B, Gutteridge JMC. Oxygen toxicity, oxygen radical, transition metals and disease. Biochem J. 1984;219:1-14.
6. Juarez Olguin H, Calderon Guzman D. Free Radicals: Formation, types and effects in Central Nervous System. In Handbook of Free Radicals: Formation, Types and Effects. Editor Dimitri Kozyrev and Vasily Slutsky ISBN: 978-60876-101-2. © 2009 Nova Science Publishers, Inc.
7. Driver AS, Kodavanti PR, Mundy WR. Age-related changes in reactive oxygen species production in rat brain homogenates. Neurotoxicol Teratol. 2000;22:175-181.
8. Wu G, Fang YZ, Yang S, Lupton JR. Glutathione metabolism and its implications for health. J Nutr. 2004;134:489-492.
9. Beckman JS, Beckman TW, Chen J, Marshall PA. Apparent hydroxyl radical production by peroxynitrite: Implications for endothelial injury from nitric oxide and superoxides. Proc Natl Acad Sci USA. 1990;87:1620-1624.
10. Valko M, Leibfritz D, Moncol J, Cronin MTD. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39:44-84.
11. Chang CY, Chen JY, Ke D, Hu ML. Plasma levels of lipophilic antioxidant vitamins in acute ischemic stroke patients: correlation to inflammation markers and neurological deficits. Nutrition. 2005;21:987-993.
12. Keeble JE, Bodkin JV, Liang L, et al. Hydrogen peroxide is a novel mediator of inflammatory hyperalgesia, acting via transient receptor potential vanilloid 1-dependent and independent mechanisms. Pain. 2009;141:135-142.
13. Watt BE, Proudfoot AT, Vale JA. Hydrogen peroxide poisoning. Toxicol Rev. 2004;23:51-57.
14. Legriel S, Marijon H, Darmon M, Lemiale V, Bedos JP, Schlemmer B, Azoulay E. Central neurological complications in critically ill patients with malignancies. Intensive Care Med. 2010;36(2):232-40.
15. Shi J, Johansson J, Woodling NS, Wang Q, Montine TJ, Andreasson K. The prostaglandin E2 E-prostanoid 4 receptor exerts anti-inflammatory effects in brain innate immunity. J Immunol. 2010;184:7207-7218.

16. Üllen A, Singewald E, Konya V, Fauler G, Reicher H, Nusshold C, Hammer A, Kratky D, Heinemann A, Holzer P, Malle E, Sattler W. Myeloperoxidase-derived oxidants induce blood-brain barrier dysfunction in vitro and in vivo. PLoS One. 2013;8(5):e64034.
17. Becaria A, Lahiri DK, Bondy SC, et al. Aluminum and copper in drinking water enhance inflammatory or oxidative events specifically in the brain. J Neuroimmunol. 2006;176:16-23.
18. Hayashi T, Juliet PA, Miyazaki A, Ignarro LJ, Iguchi A. High glucose downregulates the number of caveolae in monocytes through oxidative stress from NADPH oxidase: implications for atherosclerosis. Biochim Biophys Acta. 2007;1772:364-372.
19. Pizent A, Pavlovic M, Jurasovic J, Dodig S, Pasalic D, Mujagic R. Antioxidants, trace elements and metabolic syndrome in elderly subjects. J Nutr Health Aging. 2010;14:866-871.
20. Smirnov OA. Anemia during inflammatory processes: pathogenesis and clinical and morphological manifestations. Arch Pathol. 2010;72:56-61.
21. Guo CH, Wang CL, Chen PC, Yang TC. Linkage of some trace elements, peripheral blood lymphocytes, inflammation, and oxidative stress in patients undergoing either hemodialysis or peritoneal dialysis. Perit Dial Int. 2011;31:583-591.
22. Bao BA, Prasad AS, Beck FW, et al. Zinc decreases C-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: a potential implication of zinc as an atheroprotective agent. Am J Clin Nutr. 2010;91:1634-1641.
23. Hopkins MH, Fedirko V, Jones DP, Terry PD, Bostick RM. Antioxidant micronutrients and biomarkers of oxidative stress and inflammation in colorectal adenoma patients: results from a randomized, controlled clinical trial. Cancer Epidem Biomark. 2010;19:850-858.
24. Prasad AS. Impact of the discovery of human zinc deficiency on health. J Am Coll Nutr. 2009;28:257-265.
25. Yuan WA, Yu XJ, Liu FQ, Wang HP, Wang D. Effects of trace element supplementation on the inflammatory response in a rabbit model of major trauma. J Trace Elem Med Biol. 2010;24:36-41.
26. Vargas R, Rincon J, Pedreañez A, et al. Role of angiotensin II in the brain inflammatory events during experimental diabetes in rats. Brain Res. 2012;1453:64-76.
27. Haider L, Fischer MT, Frischer JM, et al. Oxidative damage in multiple sclerosis lesions. Brain. 2011;134:1914-1924.
28. Rajput SK, Siddiqui MA, Kumar V, et al. Protective effects of L-pGlu-(2-propyl)-L-His-L-ProNH2, a newer thyrotropin releasing hormone analog in in vitro and in vivo models of cerebral ischemia. Peptides. 2011;32:1225-1231.
29. Kalonia H, Kumar A. Suppressing inflammatory cascade by cyclo-oxygenase inhibitors attenuates quinolinic acid induced Huntington's disease-like alterations in rats. Life Sci. 2011;88:784-791.
30. Galasko D, Montine TJ. Biomarkers of oxidative damage and inflammation in Alzheimer's disease. Biomarkers Med. 2010;4:27-36.
31. Wang W, Dow KE, Flavin J. Hyperthermia amplifies brain cytokine and reactive oxygen species response in a model of perinatal inflammation. Neurosci Let. 2008;445:233-235.
32. Liu L, Chan C. The role of inflammasome in Alzheimer's disease. Ageing Res Rev. 2014;15C:6-15.
33. Puglia CD, Powell SR. Inhibition of cellular antioxidants: a possible mechanism of toxic cell injury. Environ Health Perspect. 1984;57:307–311

34. James LP, Mayeux PR, Hinson JA. Acetaminophen-induced hepatotoxicity. Drug Metab Dispos. 2003;31:1499–1506
35. Jaeschke H, Gores GJ, Cederbaum AI, Hinson JA, Pessayre D, Lemasters JJ. Mechanisms of hepatotoxicity. Toxicol Sci. 2002;65:166–176.
36. Herbert V. Prooxidant effects of antioxidant vitamins. Introduction. J Nutr. 1996;126 (4 Suppl):1197S–200S.
37. von Bernhardi R, Tichauer JE, Eugenín J. Aging-dependent changes of microglial cells and their relevance for neurodegenerative disorders. J Neurochem. 2010;112(5):1099-114.
38. William Dauer and Serge Przedborski. Parkinson´s disease: Mechanisms and models. Neuron. 2003;39:889-909.
39. Nunomura A, Tamaoki T, Motohashi N, Nakamura M, McKeel DW Jr, Tabaton M, Lee HG, Smith MA, Perry G, Zhu X. The earliest stage of cognitive impairment in transition from normal aging to Alzheimer disease is marked by prominent RNA oxidation in vulnerable neurons. J Neuropathol Exp Neurol. 2012;71(3):233-41.
40. Jomova K, Vondrakova D, Lawson M, Valko M. Metals, oxidative stress and neurodegenerative disorders. Mol Cell Biochem. 2010;345:91-104.
41. Blake DR, Hall ND, Bacon PA, Dieppe PA, Halliwell B, Gutteridge JM. Effect of a specific iron chelating agent on animal models of inflammation. Ann Rheumatol Dis. 1983;42:89-93.
42. Czapski GA, Czubowicz K, Strosznajder RP. Evaluation of the antioxidative properties of lipoxygenase inhibitors. Pharmacol Rep. 2012;64:1179-1188.
43. Sifringer M, Bendix I, von Haefen C, et al. Oxygen toxicity is reduced by acetylcholinesterase inhibition in the developing rat brain. Dev Neurosci. 2013;35:255-264.
44. Pannu R, Singh I. Pharmacological strategies for the regulation of inducible nitric oxide synthase: neurodegenerative versus neuroprotective mechanisms. Neurochem Int. 2006;49:170-182.
45. Paterniti I, Esposito E, Cuzzocrea S. Phosphodiesterases as a New Therapeutic Targets for the Treatment of Spinal Cord Injury and Neurodegenerative Diseases. Curr Med Chem 2014;16. [Epub ahead of print]
46. Prakash D, Gopinath K, Sudhandiran G. Fisetin enhances behavioral performances and attenuates reactive gliosis and inflammation during aluminum chloride-induced neurotoxicity. Neuromol Med. 2013;15:192-208.
47. Armagan G, Kanit L, Yalcin A. Effects of non-steroidal antiinflammatory drugs on D-serine-induced oxidative stress in vitro. Drug Chem Toxicol. 2012;35:393-398.
48. Mackay GM, Forrest CM, Stoy N. Tryptophan metabolism and oxidative stress in patients with chronic brain injury. Eur J Neurol. 2006;13:30-42.
49. Stoy N, Mackay GM, Forrest CM, et al. Tryptophan metabolism and oxidative stress in patients with Huntington's disease. J Neurochem. 2005;93:611-623.
50. Shi J, Wang Q, Johansson JU. Inflammatory prostaglandin E2 signaling in a mouse model of Alzheimer disease. Ann Neurolol. 2012;72:788-798.
51. Liang X, Wang Q, Hand T, et al. Deletion of the prostaglandin E2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. J Neurosci. 2005;25:10180-10187.
52. Kubera M, Obuchowicz E, Goehler L, Brzeszcz J, Maes M. In animal models, psychosocial stress-induced neuro-inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatr. 2011;35:744-759.
53. Adibhatla RM, Hatcher JF. Altered lipid metabolism in brain injury and disorders. Subcell Biochem. 2008;49:241-268.

54. Gahm C, Holmin S, Rudehill S, Mathiesen T. Neuronal degeneration and iNOS expression in experimental brain contusion following treatment with colchicine, dexamethasone, tirilazad mesylate and nimodipine. Acta Neurochir (Wien). 2005;147:1071-1084.
55. Echigo R, Shimohata N, Karatsu K, et al. Trehalose treatment suppresses inflammation, oxidative stress, and vasospasm induced by experimental subarachnoid hemorrhage. J Translational Med. 2012;10:80.
56. Piermartiri TC, Figueiredo CP, Rial D, et al. Atorvastatin prevents hippocampal cell death, neuroinflammation and oxidative stress following amyloid-β(1-40) administration in mice: evidence for dissociation between cognitive deficits and neuronal damage. Exp Neurol. 2010;226:274-284.
57. Wilkinson BL, Cramer PE, Varvel NH, et al. Ibuprofen attenuates oxidative damage through NOX2 inhibition in Alzheimer's disease. Neurobiol Aging. 2012;33:21-32.
58. Tu XK, Yang WZ, Wang CH, et al. Zileuton reduces inflammatory reaction and brain damage following permanent cerebral ischemia in rats. Inflammation. 2010;33:344-352.
59. Celik S, Erdogan S. Caffeic acid phenethyl ester (CAPE) protects brain against oxidative stress and inflammation induced by diabetes in rats. Mol Cell Biochem. 2008;312:39-46.
60. Kumari B, Kumar A, Dhir A. Protective effect of non-selective and selective COX-2-inhibitors in acute immobilization stress-induced behavioral and biochemical alterations. Pharmacol Rep. 2007;59:699-707.
61. Jesudason EP, Masilamoni JG, Ashok BS, et al. Inhibitory effects of short-term administration of DL-alpha-lipoic acid on oxidative vulnerability induced by Abeta amyloid fibrils (25-35) in mice. Mol Cell Biochem. 2008;311:145-156.
62. Shen YC, Wang YH, Chou YC, et al. Dimemorfan protects rats against ischemic stroke through activation of sigma-1 receptor-mediated mechanisms by decreasing glutamate accumulation. J Neurochem. 2008;104:558-572.
63. Wiklund L, Basu S, Miclescu A, Wiklund P, Ronquist G, Sharma HS. Neuro- and cardioprotective effects of blockade of nitric oxide action by administration of methylene blue. Ann New York Acad Sci. 2007;1122:231-244.
64. Castillo J, Leira R. Predictors of deteriorating cerebral infarct: role of inflammatory mechanisms. Would its early treatment be useful? Cerebrovasc Dis. 2001;11:40-48.
65. Jesudason EP, Baben B, Ashok BS, et al. Anti-inflammatory effect of melatonin on A beta vaccination in mice. Mol Cell Biochem. 2007;298:69-81.

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