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OPTIMIZATION OF OXIDATION FOR DOPAMINE BY HIGH-VALENT MANGANESE WITH NEURODEGENERATIVE DISORDERS

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Abstract:
The liquid phase oxidation of benzyl alcohol is an important reaction for generating Benz aldehyde and benzoic acid that are largely required in the perfumery and pharmaceutical industries.The current production systems suffer from either low conversion or over oxidation. In-built antioxidant system of body plays its decisive role in prevention of any loss due to free radicals. However, imbalanced defense mechanism of antioxidants, overproduction or incorporation of free radicals from environment to living system leads to serious penalty leading to neuro-degeneration. Neural cells suffer functional or sensory loss in neurodegenerative diseases. Apart from several other environmental or genetic factors, oxidative stress (OS) leading to free radical attack on neural cells contributes calamitous role to neuro-degeneration. Though, oxygen is imperative for life, imbalanced metabolism and excess reactive oxygen species (ROS) generation end into a range of disorders such as Alzheimer's disease, Parkinson's disease, aging and many other neural disorders. Toxicity of free radicals contributes to proteins and DNA injury, inflammation, tissue damage and subsequent cellular apoptosis. Antioxidants are now being looked upon as persuasive therapeutic against solemn neuronal loss, as they have capability to combat by neutralizing free radicals. Diet is major source of antioxidants, as well as medicinal herbs are catching attention to be commercial source of antioxidants at present.

1.0 Introduction:

Natural antioxidant system is sorted in two major groups, enzymatic and non-enzymatic. Enzymatic antioxidants are comprised of limited number of proteins such as catalase, glutathione peroxidase as well as superoxide dismutase (SOD) along with some supporting enzymes. Non-enzymatic antioxidants include direct acting antioxidants, which are extremely important in defense against OS. Most of them include ascorbic and lipoic acid, polyphenols and carotenoids, derived from dietary sources. The cell itself synthesizes a minority of these molecules. Indirectly acting antioxidants mostly include chelating agents and bind to redox metals to prevent free radical generation Manganese (Mn) is one of the most common elements in the earth's crust and an essential metal present in several dietary sources including nuts, grains, and tea The recommended dietary intake for Mn is 2.3 and 1.8 mg/day for men

and women, respectively. Critical enzymes, such as manganese superoxide dismutase (Mn-SOD) and glutamine synthetase, contain Mn in their structure which is essential for their functions Although Mn intake is necessary to maintain life, exposure to excessive amounts of this transition metal has been associated with various adverse outcomes. The chief sources of airborne Mn are industrial emissions associated with ferroalloy production, iron and steel foundries, coke ovens and power plant combustion emissions Occupational exposure to Mn-containing dust is associated with adverse respiratory, reproductive, and, importantly, neurological effects

Need of Antioxidants:

It has been reported in epidemiological studies that many of antioxidant compounds posses anti-inflammatory, antiatherosclerotic, antitumor, ant mutagenic, anticarcinogenic, antibacterial and antiviral activities to greater or lesser extent In many cases, increased oxidative stress is a widely associated in the development and progression of diabetes and its complications which are usually accompanied by increased production of free radicals or failure of antioxidant defense Though the intake of natural antioxidants has been reported to reduce risk of cancer, cardiovascular diseases, diabetes and other diseases associated with aging, there is considerable controversy in this area Leukocytes and other phagocyte destroy bacteria, parasites and virus-infected cells with NO, O_2, H_2O_2, and OCl, those are powerful oxidants and protect humans from infection. However, they cause oxidative damage and mutation to DNA and participate in the carcinogenic process if unchecked.

Sources of Antioxidants

Four endogenous sources appear to account for most of the oxidants produced by cells. (1) Normal aerobic respiration in which mitochondria consume O_2, reduces it by sequential steps to produce O_2, H_2O_2, and -OH as byproduct. (2) Bacteria or virus infected cells get destroyed by phagocytosis with an oxidative burst of nitric oxide (NO), O_2^-, H_2O_2 and OCl. (3) Peroxisomes produce H_2O_2 as a by-product of fatty acid and other lipid molecular degradation, which is further degraded by catalase. Evidence suggests that, certain conditions favor escape of some of the peroxide from degradation, consequently releasing it into other compartments of the cell and increasing oxidative stress leading to DNA damage. (4) Animal Cytochrome P_{450} enzymes are one of the primary defense systems that provides protection against natural toxic chemicals from plants, the major source of dietary toxins.

2.0 Literature review:

M. T. Lin and M. F. Beal,(2006) Human body produce oxygen free radicals and other reactive oxygen species as by products through numerous physiological and biochemical processes. Oxygen related free radicals (superoxide and hydroxyl radicals) and reactive species (hydrogen peroxide, nitric oxide, peroxynitrile and hypochlorous acid), are produced in the body, primarily as

a result of aerobic metabolism At the same time, antioxidants, such as glutathione, arginine, citrulline, taurine, creatine, selenium, zinc, vitamin E, vitamin C, vitamin A and tea polyphenols help to regulate the ROS thus generated.

Pamplona, and I. M. Ferrer,(2005) Biological tissues require oxygen to meet their energetic demands. However, the consumption of oxygen also results in the generation of free radicals that may have damaging effects on cells. The brain is particularly vulnerable to the effects of reactive oxygen species due to its high demand for oxygen, and its abundance of highly peroxidisable substrates. Oxidative stress is caused by an imbalance in the redox state of the cell, either by overproduction of reactive oxygen species, or by dysfunction of the antioxidant systems. Oxidative stress has been detected in a range of neurodegenerative disease, and emerging evidence from in vitro and in vivo disease models suggests that oxidative stress may play a role in disease pathogenesis.

G. C. Brown and V. Borutaite (2008) The disappointing translation of the oxidative stress hypothesis into useful therapy in human disease raises several issues regarding extrapolation of results from animal studies to the clinical setting. All animal models are limited in recreating the human disease as they do not recapitulate the long-time frame and gradual accumulation of age-related changes that characterise late onset sporadic neurodegenerative diseases in humans. From much of the animal model data, it appears that antioxidants must be administered at an early stage in the disease where the process influences pathogenesis most, and therefore the use of antioxidants in established late disease in humans may be ineffective.

Iguchi-Ariga, and H. Ariga(2005), Many factors can affect the performance of manganese oxide catalysts during the oxidation of benzyl alcohols, but there were only a few studies exploring the influence of calcination temperatures of precursors on the physiochemical property and catalytic activity of the final products Furthermore, plenty of materials with similar gross structure features might have various properties due to different particle sizes and the amount and type of defects formed during different synthesis procedures. So even slight changes of synthetic parameters can result in distinct properties in catalytic, electrochemical, or ion-exchange activity In this report, transition metal-manganese oxide nanoparticles have been prepared by the variation of precursors and thermally controlled calcination.

3.0 Methodology:

It was found that the composition of the precursors has significant influence on the structure formation and surface property of the manganese oxide nanoparticles. In addition, the crystallinity of the resulting manganese nanoparticles was gradually improved upon increasing the calcination temperature; however, the specific surface area decreased obviously due to pore structure damage at higher calcination temperature. The sample calcined at the optimal temperature of 600 °C from the

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precursors without porogen was a Mn_3O_4-rich material with a small amount of Mn_2O_3, which could generate a significant amount of O−2 species on the surface that contributed to the high catalytic activity in the oxidation. Adding porogen with precursors during the synthesis, the obtained catalysts were mainly Mn_2O_3crystalline, which showed relatively low activity in the oxidation. All prepared samples showed high selectivity for benzaldehyde and benzoic acid. The obtained catalysts are comparable to the commercial OMS-2 catalyst. The synthesis–structure–catalysis interaction has been addressed, which will help for the design of new high-performance selective oxidation catalysts.

Neurodegenerative diseases and oxidative stress:

Neurodegenerative diseases comprise a condition in which nerve cells from brain and spinal cord are lost leading to either functional loss (ataxia) or sensory dysfunction (dementia). Mitochondrial (Mt) dysfunctions and excitotoxicity and finally apoptosis have been reported as pathological cause for aging and neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Multiple Sclerosis (MS) and amyolotrophic lateral sclerosis (ALS). Neurodegeneration have been speculated to be interplay of a number of factors including environmental and genetic predisposition but redox metal abuse occupies central role as most of symptoms stems out from abnormal metal metabolism Oxidative stress and free radical generation catalyzed by redox metals have been shown to play pivotal role in regulating redox reactions *in vivo* contributing RNS and ROS, main culprits in neurodegeneration While considering role of oxidative stress in neurodegeneration, few important aspects need to be mentioned

Preparation of working exposure solutions

Stock 100 mM solutions of manganese chloride ($MnCl_2$) and manganese sulfate ($MnSO_4$) were prepared in ddH_2O. Stock 250 mM solutions of manganese phosphate ($MnPO_4$ hureaulite), zinc phosphate ($ZnPO_4$), and cobalt phosphate ($CoPO_4$) were prepared in concentrated HCl (12 M). These stocks were diluted to the actual working concentrations in HEPES buffered Hank's saline solution (HBHS), pH 7.4, supplemented with 1% v/v horse serum (1% HBHS). In the case of $MnPO_4$, $ZnPO_4$, and $CoPO_4$, the highest working concentration solution was adjusted to pH 7.4 with 2N NaOH. Vehicle controls contained the appropriate amount of either ddH2O or NaOH-buffered HCl. In preliminary experiments, we determined that 200 µM working solutions of $MnPO_4$ precipitate after pH adjustment and a 4 h exposure duration. Therefore, 100µM was the highest working concentration of $MnPO_4$, $ZnPO_4$, and $CoPO_4$ used in the actual experiment

Oxidative Stress Results in Selective Neuronal Degeneration:

to a global oxidative stress that affects all neurons, there must be additional factors that determine the selective cell death in each disease.Certain neuronal groups have high intrinsic levels of oxidative stress and

are therefore more vulnerable to additional disease-related oxidative stress. Neurons that have long axons and multiple synapses have high bioenergetic requirements for axonal transport or long-term plasticity. A high ATP demand combined with relative mitochondrial dysfunction will render these groups of neurons far more sensitive to degeneration than other neuronal groups. Different neuronal groups exhibit different degrees of oxidative stress. For example, in the hippocampus CA1 neurons generate higher levels of superoxide anion than CA3 neurons and exhibit higher levels of expression of both antioxidant and ROS-producing genes

4.0 Results:

Oxidative stress arises due to disturbed equilibrium between pro-oxidant/antioxidant homeostasis that further takes part in generation of ROS and free radicals those are potentially toxic for neuronal cells. The reason for neuronal cell hypersensitivity towards oxidative stress arises due to anatomic and metabolic factors. In the brain, various types of glial cells are present and these are involved in anatomic support and metabolic requirement. The endothelial cells surrounding these glial cells are less permeable for uptake of various molecules and protective cells viz. macrophages compared to other endothelial cells in the body. In addition, glial cells in brain require more oxygen and glucose consumption to generate continuous ATP pool *in vivo* for normal functioning of brain as it is one of busiest organ to keep all other organs active and under control. That makes them more susceptible towards oxygen over load, thus free radical generation Under physiological condition, 1-2% of O_2 consumed is converted to ROS but in aged brain this percentage goes up due to reduced surveillance of antioxidants and low regenerative capacity of aged brain As a first step, we sought to determine whether exposure to three different Mn compounds ($MnCl_2$, $MnSO_4$, and $MnPO_4$) would compromise the viability of the striatal tissue. Striatal slices from male Sprague Dawley rats were collected and incubated for 4 h in either control medium or in medium containing $MnCl_2$ (10, 100, and 1000 μM), $MnSO_4$ (10, 100, and 1000 μM), and $MnPO_4$ (1, 10, 100 μM). In order to assess tissue viability, media LDH levels were determined at the end of the incubation period. LDH levels remained stable across the various treatment groups with the exception of a small but significant ($P \leq 0.05$; 23%) increase at the 100μM $MnPO_4$ level

Use of Antioxidant Therapy in Neurodegenerative Disease

Based on the hypothesis that oxidative stress is pathogenic in neurodegenerative disease, the rationale for the use of antioxidants as therapies is clear. And indeed the initial demonstration of the benefits of antioxidants in animal and cell models of disease was promising. Perhaps the most widely studied of these antioxidant therapies have been vitamin E (the major scavenger of lipid peroxidation in brain), vitamin C (intracellular reducing molecule), and coenzyme Q10 (transfers electrons from

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complexes I and II to complex III in respiratory chain).Vitamin E supplementation in an AD mouse model resulted in improved cognition and reduced βA deposition The reduction of amyloid deposition was particularly noted in young AD mice Daily injections of vitamin C in the APP/presenilin 1 mouse model significantly reduced memory deficits.

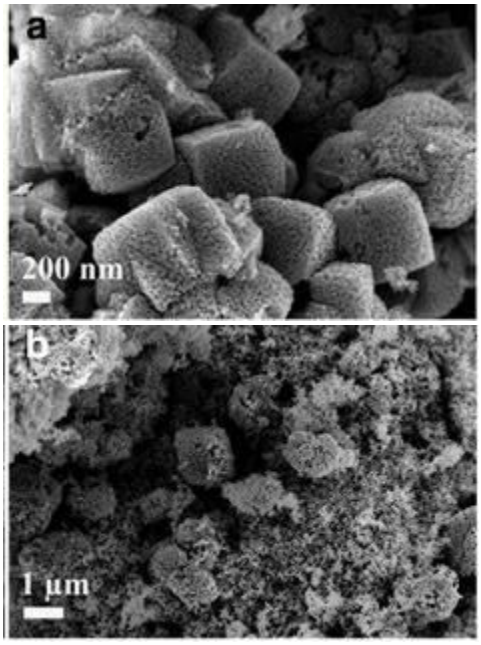
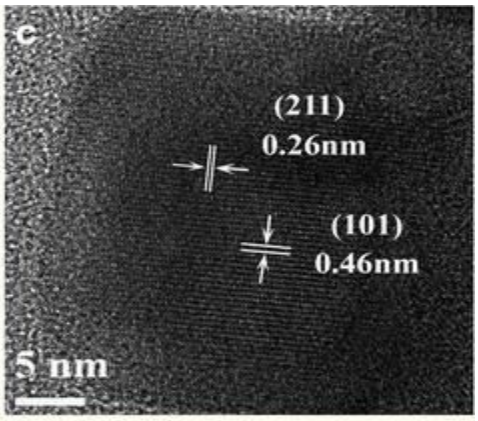


Figure: Manganese precursor SEM images of precursor S1 (**a**) and precursor S2 (**b**) calcined at 600 °C



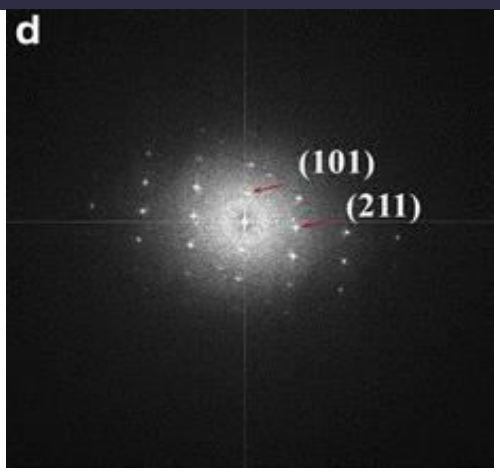


Figure: R-TEM images of manganese precursor S3 calcined at 600 °C

After calcination at 600 °C in air, the morphologies of precursor S1 and precursor S2 were apparently different from that of precursor S3. Mesopores have been observed in the cubic particles, and all the lattice planes in d can be indexed to bixbyite Mn_2O_3. Therefore, crystalline Mn_3O_4 was formed for S3 and crystalline Mn_2O_3 was formed for S1 and S2 after the 600 °C calcination. The compositions for the preparation of precursors had significant influence on the structure formation of manganese oxide nanoparticles.

Pathological Evidences of ROS Mediated Neuronal Damage:

Neuronal biochemical composition is mainly susceptible to ROS since it involves pool of unsaturated lipids those are labile to peroxidation and oxidative modification. Double bonds of unsaturated fatty acids are hot spots for attack by free radicals those initiate cascade or chain reaction to damage neighboring unsaturated fatty acids Several researchers considered brain to be abnormally sensitive to oxidative damage

and many studies demonstrative of the ease of peroxidation of brain membranes supported this notion Brain contains high level of fatty acids which are more susceptible to peroxidation, that consumes an inordinate fraction (20%) of total oxygen consumption for its relatively small weight (2%). In addition, it is not particularly enriched in antioxidant defenses. Brain is lower in antioxidant activity in comparison with other tissues, for example, about 10% of liver.

Genetic Evidences in Neuro degenerations and Oxidative Stress:

Oxidative stress related neuro degeneration is not only caused by disturbed metal metabolism but genetic evidences suggests that persons associated with certain types of genetic mutations are more susceptible to gain neurological pathological compare to normal to those with normal genetic profile. Person with hemochromatosis (HFE) associated mutations may be on higher side of developing iron over load related oxidative stress and neuropathology with ingestion of daily iron supplement Metal metabolism is combined interplay between genes related with synthesis of metalloenzymes and dietary metal supplement. Any imbalance in this interaction favors dysregulated cellular metallobiology that subsequently leads to neurodegenerations. Clinicians suggests it is made to be mandatory to counsel the patients with associated mutations and increased risks of neuro degeneration.

Conclusion: Neuronal proteins and structural components get modified due to OS in different neurological disorders leading to neuro-inflammation and loss of cognitive function in AD, PD, MS and ALS. Since in this review, OS have been defined as principle pathological cause of neurodegeneration, antioxidants are proposed as therapeutic options to combat the free radical generation and maintenance. This review covers the sources of antioxidants and free radicals and general mechanism involve in antioxidant mediated free radical scavenging. Major emphasis have been given on the role of oxidative stress and free radical chemistry with respect to major neurodegenerative disorders The oxidation activities of the samples were not increased proportionally with the surface area but were correlated to the crystal structure and surface sites. S3-600 with the significant amount of O−2 species on the surface during oxidation exhibited the highest catalytic activity in the oxidation of alcohols. S1 and S2-600 with mainly crystalline Mn_2O_3 could contain the dominant lattice oxygen O^{2-}, surface O^{-}, or β-oxygen species on the surface that led to the relatively lower activity in the oxidation.

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