Review Article *Open Access*

Journal of Advanced Clinical Neurology Research

ISSN:3071-0731

DOI: *doi.org/10.63721/26JACNR0114*

Targeting Mechanistically Interaction Amongst Neuron-Glia Redox Signalling Subsequent to CNS Damage/ Neurodegenerative Diseases (NDD) Generation: Specifically Astrocytic Antioxidant Mechanistic Modes -A Review

Kulvinder Kochar Kaur[1*], Gautam Nand Allahbadia[2] and Mandeep Singh[3]

[1]Obstt & Gynae, specialist reproductive endocrinology & Infertility specialist, Punjab, India
[2]Obstt & Gynae, Ex-Rotunda-A Centre for Human Reproduction Mumbai, India
[3]Consultant Neurologist Swami Satyanand Hospital, Punjab, India

Citation: Kulvinder Kochar Kaur, Gautam Nand Allahbadia, Mandeep Singh (2026) Targeting Mechanistically Interaction Amongst Neuron-Glia Redox Signalling Subsequent to CNS Damage/ Neurodegenerative Diseases (NDD) Generation: Specifically Astrocytic Antioxidant Mechanistic Modes -A Review. J of Adv Clin Neu Res 2(1), 01-34. WMJ/JACNR-114

Abstract

Astrocytes possess a pivotal part in sustenance of redox harmony and assisting neuronal survival amongst the central nervous system (CNS). Their antioxidant machinery, mainly implicating i) Nrf2-ARE (nuclear factor erythroid 2-related factor 2-antioxidant response element) pathway, ii) glutathione (GSH) metabolism, and iii) mitochondrial working, making iv) elimination of reactive oxygen and nitrogen species (ROS and RNS) advocate neuronal resistance to oxidative stress (OS). Efficacious connection amongst neurons and astrocytes aligns metabolic and antioxidative reactions through i) glutamate-, ii) nitric oxide-, and iii) calcium- based signalling. Disturbance of such interaction at the time of i) traumatic brain injury (TBI), ii) ischemia, or iii) neurodegenerative diseases (NDD) results in i) redox dysequilibrium, ii) neuroinflammation, and iii) excitotoxicity, which allow propagative ND. Astrocytic Nrf2 activation diminishes oxidative injury and inflammation, whereas its reppression optimises the generatio of a neurotoxic glial phenotype. Present corroboration highlights variable therapeutic approaches targeting astrocytic redox mechanistic modes, like i) small-molecule Nrf2 activators, ii) GSH precursors, iii)) mitochondria-targeted antioxidants (MTAs), iv) RNA- and v) gene-dependent strategies. Such arbitrations i) buttress antioxidant capability of astrocytes, ii) impact reactive cell phenotypes, and ii) embrace neuronal rectification in preclinical models. Despite, even now the botherations are present i) in administration ii) safety, iii) and resolution of neuron-glia redox signalling yields favourable approach for neuroprotective therapies having objective of OS - associated CNS damage and disease propagation. With the advent of modes of cell demise inclusive of ferroptosis, autophagy(mitophagy), getting insight has become easy regarding targeting its constituents like xc− system (cystine/glutamate antiporter), autophagy factor ATF4 (activating transcription factor4; replenishment of GSH pool by cysteine precursors, for instance N-acetylcysteine (NAC), escalating antioxidant GSH, agents targeting antioxidant enzymes, for instance a) HO-1 and b) NQO1 diminishing OS markers, lipid peroxidation, mitochondrial ROS etc , mitoQ etc

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***Corresponding author:** Kulvinder Kochar Kaur, Obstt & Gynae, specialist reproductive endocrinology & Infertility specialist, Punjab, India.

Submitted: 25.01.2026 **Accepted:** 29.01.2026 **Published:** 15:02.2026

Keywords: Astrocytes, Nrf2-ARE, Antioxidant Mechanistic Modes, CNS Damage, Ferroptosis

Introduction

The central nervous system (CNS) is considerably prone to oxidative stress (OS), ii) a state that takes part owing to, dysequilibrium amongst the generation of reactive oxygen as well as nitrogen species (ROS as well as RNS) in addition to iii) cellular antioxidative mechanistic modes.

Plethora of ingrained characteristics of the CNS enables it specifically i) susceptible to oxidative damage: ii) neurons utilize remarkably greater quantities of oxygen in reference to sustenance of their greater metabolic actions, iii) possess enrichment of polyunsaturated lipids iv) which possess the capacity of getting oxidized with ease along with the v) overall antioxidant capability of the brain is germanely restricted in contrast to other tissues. Once accrual of ROS as well as RNS takes place further than physiological amounts, they influence i) proteins, ii) lipids, in addition to iii) nucleic acids, iv) resulting in disturbance of membrane coherence, v) enzyme working,along with vi) genetic stability.2) Sequentially, OS has appeared in the form of a i) central as well as ii) integrating pathological mechanistic modes iii) aiding in a broad spectrum of neurological conditions, inclusive of i) ischemic stroke, ii) traumatic brain injury (TBI), iii) chronic neurodegenerative diseases(NDD), in addition to iv) inflammatory disorders. Despite, such diseases i) might vary in their initiation along with ii) propagation, they share iii) plethora of merging molecular pathways, maximum pronouncedly i) mitochondrial impairment, ii) excitotoxicity, iii) inflammation, as well as iv) oxidative damage which result in neuronal demise in addition to diminished working [1-3].

Mitochondria delineate both a i) main facility along with a ii) target of oxidative injury, iii) in the form of dysequilibrium in the electron transport chain iv) escalates ROS formation, v) further destabilizing mitochondrial coherence as well as vi) energy metabolism. 2) In neurons, i) glutamate excitotoxicity which takes place ii) causes intensified triggering of its receptors, iii) escalates intracellular calcium in addition to iv) stimulates activation of enzymes that a)generate free radicals, b)further aiding in propagative neurological inimicality [4,5]. Amongst such circumstances astrocytes possess i) an elemental along with ii) heterogeneous part in iii) sustenance of redox equilibrium as well as iv) conferring protection to neurons from oxidative injury.

In the form of maximum enriched glial cell kinds, astrocytes yield imperative i) metabolic in addition to ii) antioxidant embracing to neurons, iii) control extracellular ion, along with iv) neurotransmitter quantities, v) actions as well as vi) produce constituent of the blood–brain barrier (BBB). Their antioxidant systems are specifically potent, inclusive of greater amounts of i) glutathione (GSH), ii) superoxide dismutase (SOD), iii) catalase (CAT), as well as iv) GPx (GSH peroxidase) [6-9].

II)Subsequent to failing of astrocytic redox controlling, ii) neurons assume specific susceptibility to oxidative damage. In cerebral ischemia, the abrupt cutting off of blood flow leads a) to elimination of oxygen as well as b) glucose, to neural tissue swiftly c) influencing ATP generation. The resulting lesser energy provision i) disrupts ionic homeostasis, resulting in ii) accelerated glutamate liberation. The sequential calcium influx stimulates the activation of enzymes for instance i) nitric oxide synthase, ii) phospholipases, in addition to iii) proteases, total of that allow for the generation of ROS, along with RNS.

Following reperfusion, the sudden reestablishment of oxygen further aggravates OS by escalating i) mitochondrial electron leakage as well as ii) activating xanthine oxidase. Such oxidative burst leads to i) lipid peroxidation, ii) mitochondrial collapse, in addition to iii) eventually neuronal demise through a) necrosis,

along with b) apoptosis [10-12]. An analogous redox- guided series takes place in TBI as well as spinal cord injuries (SCI). The beginning mechanical injury generate prompt structural damages in addition to vascular disturbance, followed by a secondary phase which possess the characteristics of i) mitochondrial impairment, ii) calcium decontrolling, along with iii) considerable oxidative along with iv) inflammatory activation.Microglia as well as infiltrating immune cells liberates i) ROS, ii) RNS, in addition to iii) proinflammatory cytokines, augmenting tissue damage further than the initial disfigurement region. Continued OS subsequent to trauma apart from i) escalating deterioration of acute neuronal elimination, further facilitates ii) chronic neuroinflammation, along with iii) causing postponement of neurodegeneration, that pivotally allow for long-term neurological deficiencies [13,14].

OS is further a defining landmark of chronic neurodegenerative conditions for instance, i) Alzheimer's disease (AD), ii) Parkinson's disease (PD), as well as iii) amyotrophic lateralsclerosis (ALS). In such disorders, i) continued mitochondrial impairment, ii) dysfunctional protein breakdown, in addition to iii) accrual of misfolded proteins results in maintained ROS production [5,15]. i) In PD, for example, a) dopamine oxidation along with b) mitochondrial complex I dysfunction c) generate free radicals which in a selective manner d) lead to injury to the dopaminergic neurons in the substantia nigra [16]. ii) In AD, a) β-amyloid peptides catalyze ROS generation, b) interfere with mitochondrial working,c) as well as hamper antioxidant enzymes, d) further facilitating neuronal demise [17].

Correspondingly, a) oxidative modification of lipids in addition to b) proteins c) disrupts synaptic connection, along with d) signal transduction, e) bolstering the degenerative event.III) Inflammation delineates one additional robust guiding force of OS amongst the CNS. Activated i) microglia in addition to ii) astrocytes generate iii) ROS, along with iv) RNS in the form of partial immune reactions to a) damage or b) infection. Whereas transient activation possesses the capability of i) conferring protection to neurons, ii) promoting clearance of garbage as well as tissue healing, iii) chronic activation results in sustained OS in addition to nitrosative stress [18,19]. Such escalated oxidative injury in neurons, along with further activates glial cells, generating a vicious cycle of inflammation as well as OS. In such complicated network of crosstalks,neuron–glial connection incepts in the form of a pivotal factor in sustenance of astrocytic antioxidative defence in addition to total redox homeostasis. Astrocytes persistently adapt their metabolic, along with antioxidant reactions in as per neuronal activity as well as metabolic needs [8].

Metabolic crosstalks amongst a) neurons as well as b) astrocytes further c) accounts for the sustenance of redox homeostasis. d) On disturbance of neuron–glial signalling, e) the adaptive antioxidant reactions of astrocytes gets dysfunctional, leading to i) redox imbalance in addition to ii) neuronal susceptibility. In neurodegenerative diseases (NDD), iii) elimination of neuronal tips iv) reduces astrocytic metabolic alignment, v) diminishing the capability to neutralize ROS. Sequentially, OS becomes self- perpetuating, guiding further neuronal demise, along with escalated disease propagation [2,20].

OS delineates a central as well as shared pathogenic mechanistic modes in practically all kinds of CNS damage. Astrocytes, via their metabolic resilience in addition to, antioxidant capability, work in the form of fundamental controllers of neuronal redox homeostasis. Their working, however, is based robustly on, indelible connection with neurons. Several reviews have summarized astrocytic antioxidant mechanistic modes. This review offers a conceptual synthesis that highlights the dynamic neuron–glia redox dialogue in the form of a central event shaping cellular reactions subsequent to CNS injury. Apart from previously detailed reviews that basically emphasized intracellular Nrf2–Keap1 (nuclear factor erythroid2-related factor 2–Kelch-like ECH-related protein 1) signalling, we gather corroboration from plethora of cell kinds to posit a model of cross-cellular redox alignment associating i) astrocytic, ii) neuronal, as well as iii) microglial antioxidative event networks.

Previously we reviewed the pivotal part of OS in the generation of NDD for instance ALS, AD, PD, part of Gut Microbiota dysbiosis in NDD generation as well as ischaemic Stroke development, Role of Bile Acids in NDD generation inclusive of ALS, AD, PD, HD in addition to priondisease. Additionally, recently we updated variable mechanistic modes of cell demise

in Breast cancer (BC) along with variable cancers Mitophagy Facilitating Substances specifically regarding therapies of NDD apart from cancer, ovarian Ageing. Furthermore, we highlighted part of Interactions Amongst Endoplasmic Reticulum Stress and Ferroptosis regarding ovarian cancer treatment which got followed by part of Ferroptosis in treatment of Diabetic Kidney Disease where we detailed nuclear factor erythroid-2-related factor-2((Nrf2) / Kelch-like-epichlorohydrin (ECH)-associated protein 1 (KEAP1) thoroughly. Earlier we had detailed ROS , along with RNS generation in case of acute kidney injury &role the utilization of N-acetyl cysteine & vitamin c for tackling the OS stress in acute kidney injury secondary to robust sepsis & recently N-acetyl cysteine utilization for addressing OS, Ferroptosis in Polycystic ovary syndrome (PCOS) and detailed complete wnt-β catenin signalling system with its constituents in osteoporosis &cancer,which are implicated in neuron-glia redox signalling as well [21-39].Here our aim in this review is to emphasizes the manner intercellular metabolic coupling in addition to signal transduction together impact the efficacy of redox manipulation, yielding a new systems-level perspective which incorporates i) molecular, ii) cellular, along with iii) plausible translational ingredients of antioxidant neuroprotection. Getting insight as well as escalating such neuron–astrocyte interactions provide meaningful therapeutic plausibility i) by inducing Nrf2 signalling, ii) buttressing astrocyte metabolism, iii) or resulting in rectification of neuron–glial metabolic coupling, which possesses the capability of causing substantial improvement of the brain's adaptability to OS, specifically subsequent to CNS damage. Thereby, perpetuating the dynamic reciprocity amongst neurons in addition to glial cells apart from elemental in reference to sustenance of CNS homeostasis however further mirrors an attractive trajectory for future neuroprotective arbitrations.

Machinery in Reference to Antioxidant Astrocytic Actions

The phase II antioxidant reactions are inclusive of i) detoxifying as well as ii) antioxidant enzymes,whose expression is stimulated solely by i) de novo transcription in addition to ii) is regulated by the transcription factor nuclear factor erythroid-2-related factor 2 (Nrf2, encoded by NFE2L2). The Nrf2 factor activates the antioxidant reactions through crosstalk with the ARE (antioxidant response element) of Nrf2-targeted genes. Acknowledged this, Nrf2 is believed to be a master governer of antioxidant defence [40]. Nrf2 portrays a transcription factor sensitive to cellular redox status, creating heterodimers with MAF (Musculo aponeurotic fibrosarcoma) family proteins, that accounts for their acknowledgement, along with binding to DNA regulatory emblems [8].

The Nrf2 factor is comprised of 605 amino acid residues, forming seven domains (Neh1–Neh7). i) The Neh1 domain (435–562 aa) possesses a DNA-binding design, which enables Nrf2 to crosstalk with other transcription factors. ii)Furthermore, Neh1 stabilizes Nrf2 by binding to the ubiquitin-conjugating enzyme UbcM2. i) The basic working of the Neh2 domain, which possesses placement at the N-terminus of Nrf2, is crosstalking with Keap1. ii) Neh3 (562–605 aa), 4, as well as5 (112–134 aa) are held responsible in Nrf2 transactivation through crosstalks with coactivators.

Particularly, Neh 3 i) crosstalks with the coactivator chromo-ATPase/helicase DNA-binding protein family member CHD6 (chromo-ATPase/helicase DNA-binding protein 6), ii) while Neh 4 in addition to 5, iii) along with Neh 5crosstalk with the CH3 domain of CBP (CREB-binding protein) [41]. Two patterns in Neh 6 (338–388 aa), DSGIS as well as DSAPGS, bind to the β-transducing repeat containing protein (β-TrCP). Such protein serves in the form of a substrate adaptor for the Skp1/CUL1/Rbx1Roc1ubiquitin ligase complex. The DSGIS motif in Neh 6 is phosphorylated by GSK-3 (glycogensynthase kinase 3), which enhances β-TrCP to ubiquitin- based breakdown of Nrf2.Moreover, the Neh 7 domain binds to retinoic X receptor alpha (RXRα) in addition to, represses the transcription of Nrf2 target genes [42,43] (Figure 1). [rev in 44]

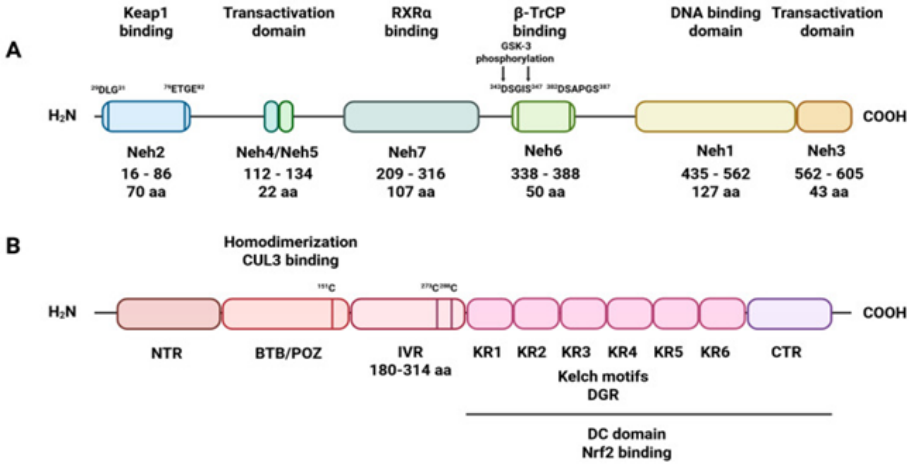


Figure 1: Courtesy ref no-44 Schematic diagram of Nrf2 and Keap1 domains. (A) Nrf2 possesses seven primary domains, namelyNeh1–Neh7. i) The Neh1 domain, part of the leucine zipper motif's basic site, impacts. i) stability, ii) DNA binding, as well as iii) sMAF dimerization. Neh2 possesses two crosstalk areas: i) the DLG motif (DLG) in addition to ii) the ETGE tetrapeptide motif (ETGE), that promotes binding to Keap1. i) The Neh4, ii) Neh5, along with iii) Neh3 domains are implicated in Nrf2 transactivation. The serine- enriched rich Neh6 domain controlling controls Nrf2 stability; (B) Keap1 possesses three main domains. i) The BTB domain mediates a) Keap1 homodimerizationin addition to b) its crosstalk with CUL3. ii) The IVR domain inclusive of a vital cysteine residue which bridgesthe BTB domain to the C-terminal Kelch/DGR domain. The Kelch/DGR domain binds Nrf2 via theNeh2 area.)

In case OS does not get escalated, the Nrf2 factor is targeted for breakdown by its endogenous hampering agent Keap1 through ubiquitin- modulated pathways [45,46]. Keap1 gets composed of 627 amino acid residues as well as is part of the Kelch family, that possesses a terminal BTB/POZ domain [47]. The Keap1 protein contains amongst its structure five domains, for instance the i) C-terminal region (CTR), ii) double glycine repeats (DGR), iii), tramtract in addition to bric-a-brac (BTB)domain, iv) the N-terminal region (NTR), in addition to v) the intervening region (IVR), that are vital for Keap1 molecular working [48] (Figure 1). The six repeated/consecutive Kelch logos (KR1-KR6) are situated in the DGR domain along with generate a six-bladed propeller structure. The DGR as well as CTR domains together generate the DC domain, that is imperative for Neh2 binding to Nrf2 [49].

The next structural ingredient pivotal for the ii) antioxidative characteristics of Keap1 is the IVR domain (180–314 aa). The IVR has placement amongst the BTB as well as DGR domains in addition to possesses abundance of cysteine residues, that, in case of OS, go through oxidation along with alkylation.

Particularly, manipulating cysteine 151, cysteine 273, along with cysteine 288 changes the configuration state of the Keap1 protein, that actually results in the detachment of Nrf2 from the Nrf2/Keap1 complex [50]. Sequentially, the released Nrf2 factor translocates from the cytosol to the nucleus, where, in case of heterodimerization with small MAF (sMAF), it stimulates the expression of antioxidative reaction genes [51]. The antioxidative reaction activated by Nrf2 needs the existence of the ARE element, with the consensus sequence 50-TGACxxxGC-30, observed in the promoters of Nrf2 target genes [52] (Figure 2).

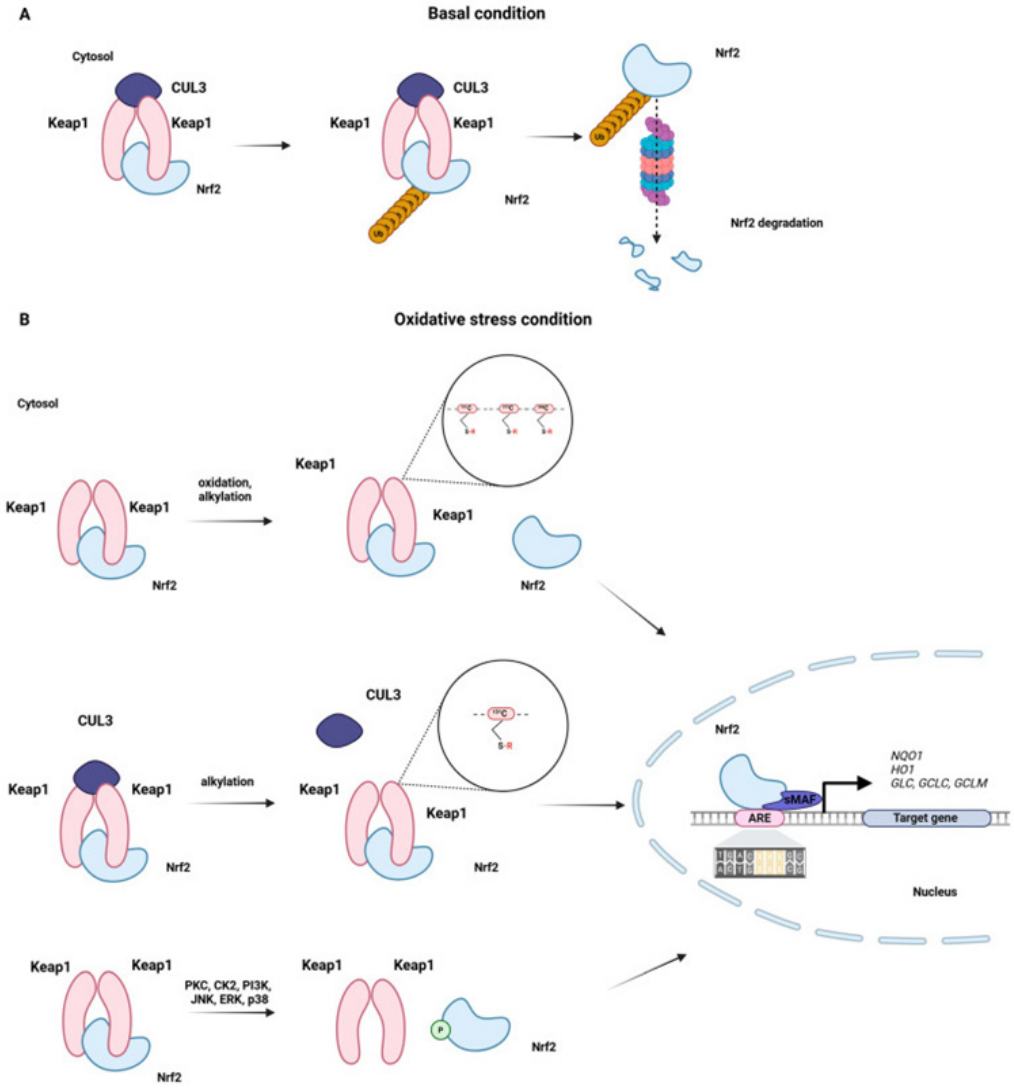
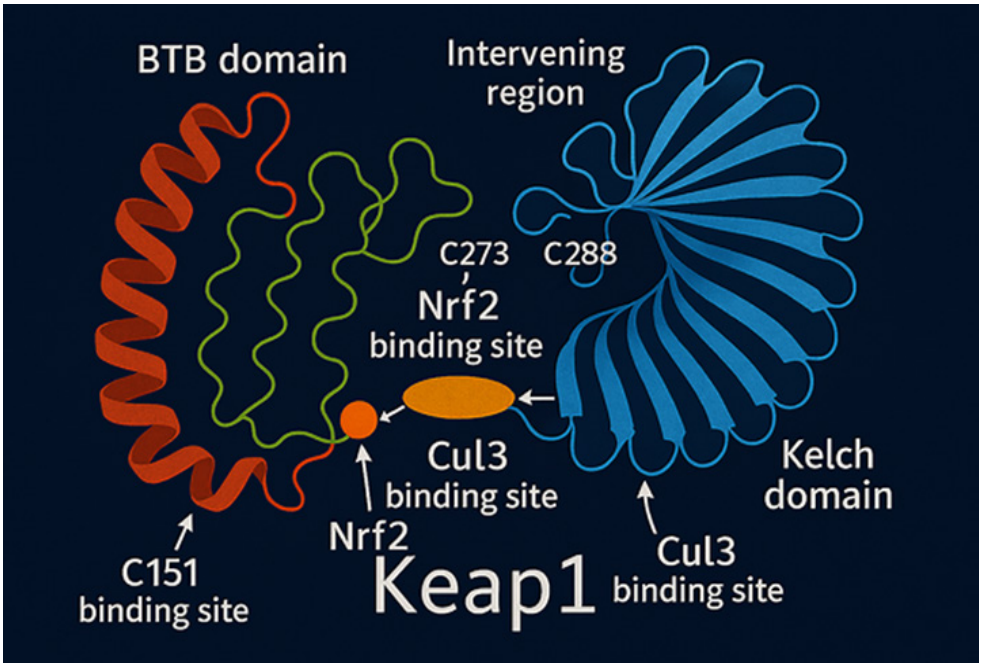


Figure 2: Courtesy ref no-44 -The schematic illustrates the Nrf2–Keap1 signalling pathway. (A) In case of basal situations, Keap1 binds to the ETGE as well as DLG emblems on Nrf2, which allow Nrf2 to join the Keap1–Cul3 ubiquitinligase complex, that tags Nrf2 for breakdown through the proteasome. (B) Under oxidative stress (OS) situations, a stimulater (oxidation or alkylation) modifies a pivotal cysteine on Keap1, which results in disturbance Keap1′s hampering complexes in addition to causes avoidance of Nrf2 ubiquitination. This modification results in a configuration change in Keap1, liberating Nrf2 along with causing avoidance of its ubiquitination, aiding it to evade breakdown. Nrf2 then translocates into the nucleus, binds to the ARE, as well as activates genes which encode i) NQO1, ii) HO-1, in addition to iii GCL subunits C along with M, buttressing cellular defences against OS. Owing to that OS, i) PKC, ii) CSK2, iii) PI3K, iv) JNK, v) ERK, in addition to vi) p38 possess the capacity of triggering phosphorylation correlated translocation of Nrf2 to the nucleus. NQO1: NAD(P)H quinone dehydrogenase (), HO-1: heme oxygenase 1 of GLC: glutamate-cysteine ligase; C: catalytic subunit; M: modifier subunit



3-D-three-dimensional structure of Keap1

Nuclear translocation of Nrf2 takes place via the importin-alpha 5/importin-beta1 import pathway [53]. Nrf2 has NESzip emblem, the nuclear export signal co- placed with the leucine zipper (ZIP) domain. On combination of Nrf2 with sMAFG via a ZIPZIPcrosstalk, it escalates the detention of Nrf2 in the nucleus. The sMAFG- modulated retention of Nrf2 in the nucleus causes avoidance of its proteasomal breakdown as well as results in stabilization of Nrf2 signalling [54]. ii) One additional mechanistic mode embracing the hampering of Keap1 implicates the binding of Keap1 to the CUL3/RBX1 complex. iii) Amongst the Keap1/CUL3RBX1/E3 ubiquitin ligase complex, i) Keap1 serves in the form of a substrate adaptor, ii) binding to RBX1 via the CUL3 scaffold. iii) On the binding of Nrf2 complex with Keap1, it results in the ubiquitination of Nrf2. Keap1 crosstalks with CUL3 via cysteine 151 in the BTB domain. Modifications for instance i) alkylation or ii) oxidation of cysteine 151 change the structure of the BTB domain of Keap1. It causes disruption of the crosstalk amongst Keap1 in addition to CUL3. Such state results in barricading of Keap1, resulting in the escape of Nrf2 ubiquitination [55] (Figure 2).

i) Apart from direct manipulation of cysteine residues in Keap1, ii) the Nrf2 shuttling to the nucleus possesses the capability of getting stimulated by the activation of kinases in reaction to the i) electrophilic or ii) oxidative stimuli. Activated kinases phosphorylate Nrf2 at serine as well as threonine residues, that promotes the separation of the Nrf2/Keap1 complex. Phosphorylation- associated translocation of Nrf2 to the nucleus possess the capacity of getting modulated by i) protein kinase C(rev in 38), ii) casein kinase2(rev in 39),iii phosphatidylinositol 3-kinase, iv) PKR-like endoplasmic reticulum kinase(rev in 35), v) JNK (c-Jun Nterminalkinase), vi) ERK (extracellular signal-regulated kinase), vii) p38 MAPK (mitogen-activated protein kinase), in addition to AMP-activated protein kinase. Conversely, GSK-3 negatively controls Nrf2 actions by phosphorylating variable regions [56,57] (Figure 2). GSK-3 modulated Nrf2 phosphorylation guides Nrf2 to proteasomal breakdown [58].

The Nrf2-ARE axis sustains antioxidative homeostasis in astrocytes by activating a myriad of antioxidant genes, which encode i) NAD(P)H quinone dehydrogenase (NQO1), ii) heme oxygenase 1 (HO-1), along with the iii) two subunits of glutamate-cysteine ligase (GLC), GCLC (γ-glutamate-cysteine ligase catalytic subunit) as well as GCLM (γ-glutamate-cysteine ligasemodifier subunit), involved in GSH generation. Additionally, Nrf2 further activates i) GPx, ii) GSH Stransferases(GST), iii) peroxiredoxins (Prx), iv) thioredoxins (Trx), v) thioredoxin reductases (TrxR), in addition to vi) NADPH (nicotinamide adenine dinucleotide phosphate—reduced

form) regenerating enzymes [59, 35-37] (Figure 2). Apart from the abovementioned genes, Nrf2upregulates SQSTM1 (sequestosome 1), that encodes p62, a protein implicated in autophagy [60].

Astrocytes possess a pivotal part in sustenance of glutamate homeostasis, that, in turn, impacts the orchestration of controlling excitatory amino acids. They further aid in avoidance of excitotoxicity by liberation of neurotrophic factors for instance i) glial-cell-line-derived neurotrophic factor (GDNF) as well as ii) nerve growth factor (NGF), that facilitates neuronal survival [61,62]. At the time of OS, astrocytes are conferring protection to neurons by generating antioxidant substances for instance i) GSH, ii) ascorbate, in addition to iii) vitamin E, along with by iv) activating enzymes that neutralize ROS, inclusive of i) GST, ii) GPx, iii) TrxR, as well as iv CAT. This facilitates superior neuronal survival [63–65]. GSH absorption takes place by neurons from the extracellular space directly or degrade it with utilization of extracellular neuronal aminopeptidase N to generate form glycine in addition to cysteine [66]. It has been corroborated that GSH-dissipated astrocytes illustrate d diminished s neuronal protection against oxidative damage, owing to neurons possess absence of adequate substrates for GSH generation [67]. By strengthening their capability of absorbing cysteine, astrocytes escalate their capability of generating GSH, that consequently reinforces their neuroprotective actions against OS [68].

Astrocytic defence against antioxidants further implicates i) ascorbate recycling, that possesses the capability of ii) eliminating ROS directly along with iii) further recycling of iv) oxidized vitamin E as well as v)GSH [69].2) Recycled ascorbate is utilized i) amongst astrocytes or ii) liberated into the extracellular space, iii) where neurons possess the capacity of its utilization in the form of an aspect of their own antioxidant defence system. In neurons,ascorbic acid hamper i) glucose utilization in addition to ii) induces lactate transport. iii) Ascorbic acid manipulates the astrocyte-neuron lactate shuttle; furthermore, neurons form glutamate, that induces astrocytes to liberate ascorbic acid in glutamatergic synaptic actions [70–72].

Astrocytes, in view of their greater expression of metallothioneins as well as ceruloplasmin, that are implicated in metal binding in addition to ion swapping, further possess a pivotal part in segregating metal ions, thereby causes avoidance of the formation of free radicals by redox-active metals [73,74, 35-37].

Neuron–Astrocyte Interaction in Redox Controlling

Contrasting Nrf2 expression amongst astrocytes along with neurons documents an exactitude design.Astrocytes possesses the characteristics of 100–1000- times greater Nrf2 quantities in contrast to neurons [75]. Nrf2- based antioxidative potential of astrocytes was corroborated in animal models,where Nrf2- insufficient mice possessed the susceptibility to OS in contrast to wild- kind animals. Intriguingly, Nrf2 extirpation in cortical neurons did not alter their restricted capability of conferring protection against oxidative damages, making them unreactive to Nrf2 activators [76,77]. Nevertheless, Nrf2 expression apparently is imperative for the appropriate generation of young neurons,that is, analogous to astrocytes, do not show epigenetic inactivation of Nrf2. Mature neurons illustrate meaningfully lesser amounts of Nrf2 promoter histone H3 acetylation in contrast to astrocytes.

Suppression of the NFE2L2 gene takes place early in neuron generation. In live animals at birth as well as in cells cultured for 2 days, Nrf2 expression in addition to pathway activity are analogous to the ones in astrocytes. Nevertheless, by day 9 in culture, Nrf2 expression is repressed, along with the promoter possesses lesser H3 acetylation [76]. One additional mechanistic mode that lies beneath neuronal unreactiveness to OS is that neurons illustrate a higher capability of Nrf2 breakdown, based on CUL3 [75]. The inimical antioxidant defence in neurons can be ascribed to the part of redox signalling in neuronal generation d [78,79]. The structural as well as electrophysiological generation of neurons subsequent to ectopic expression of Nrf2 apparently takes place from the repression of vital generational signalling pathways, inclusive of JNK as well as Wnt (wingless/integrated), whose action s is escalated by redox signalling [80–83]. No such corroboration is found in astrocytes, where predominant Nrf2 expression escalates the antioxidative buffer capability without

influencing their generation [84].

Restricted Nrf2/ARE action in neurons results in considerably lesser CAT in addition to GSH expression quantities. Such antioxidative machinery constituents are strictly based on activation of Nrf2 pathway. In both cases, Nrf2 controls the expression of CAT as well as induces the transcription of vital genes implicated in GSH biogeneration in addition to regeneration [85,86]. Actually, the expression of CAT, along with GCLC in cortical neurons is meaningfully lesser in contrast to that in astrocytes.

Neurons are substantially metabolically active cells which impose a greater need for ATP, that is imperative for sustenance of their membrane resting potential [87]. At the time of evolution,astrocytes have generated distinct i) morphological along with ii) physiological characteristics that embrace the appropriate working of neurons. iii)They possess the capability of picking up substrates from the blood as well as metabolize them for local administration to active synapses, thereby maintaining neuronal working.

The basic part of neurons in the CNS is neurotransmission, which is apart from a substantially energy- draining event however, further develops a considerably greater quantity of reactive oxygen species (ROS) basically, linked to i) Ca2+ influx in addition to ii) glutamatergic stimulation [88–90]. Interaction amongst neurons, along with astrocytes is associated with glucose metabolism. Apart from astrocytes, neurons are based on the pentose phosphate pathway (PPP) for their glucose utilization.

Such pathway contributes to regenerate NADPH quantities, which are imperative for efficacious diminishing in GSH, the brain's maximum enriched antioxidant [91–93].

Neurons further depend on GSH biogenerational machinery to regenerate GSH despite in lesser quantities, by utilization of amino acid precursors that takes place from the breakdown of astrocytic GSH [94–96]. Astrocytes liberate GSH in reaction to OS stimuli.GSH in addition to glutathione disulfide (GSSG) liberation from astrocytes implicates the multi drug resistance protein 1 (Mrp1) transporter solely, however not Mrp5 (multidrug resistanceprotein 5) [97]. GSH precursors segregated in the extracellular space are apart from getting utilized to forage ROS, however, further shuttle into nearby neurons [98,99].

Research further implies that astrocytes might possess a vital part in conferring protection to neurons from ROS- stimulated damage by clearing injured mitochondrial membranes. Such mechanistic modes plausibly are inclusive of transmitophagy, an event by whose working mitochondria are transferred from astrocytes to neurons, where they yield the defence machinery for neurons [100]. The abovementioned occurrence was detailed in the stroke model; however,till now, it continues to be queried, as the found injured mitochondria might have initiated from neuron-associated astrocytes instead of neurons [101, 102]. Conversely, it was validated that free fatty acids (FFA)generated in the breakdown of neuronal mitochondria possess the capacity of getting transferred in ApoE+ (apolipoprotein E) lipid complexes to astrocytes, where the astrocyte mitochondrial β-oxidation pathway possesses the capability of metabolizing them [103] (Figure 3).

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Neurons further depend on GSH biogenerational machinery to regenerate GSH despite in lesser quantities, by utilization of amino acid precursors that takes place from the breakdown of astrocytic GSH [94–96]. Astrocytes liberate GSH in reaction to OS stimuli.GSH in addition to glutathione disulfide (GSSG) liberation from astrocytes implicates the multi drug resistance protein 1 (Mrp1) transporter solely, however not Mrp5 (multidrug resistanceprotein 5) [97]. GSH precursors segregated in the extracellular space are apart from getting utilized to forage ROS, however, further shuttle into nearby neurons [98,99].

Research further implies that astrocytes might possess a vital part in conferring protection to neurons from ROS- stimulated damage by clearing injured mitochondrial membranes. Such mechanistic modes plausibly are inclusive of transmitophagy, an event by whose working mitochondria are transferred from astrocytes to neurons, where they yield the defence machinery for neurons [100]. The abovementioned occurrence was detailed in the stroke model; however,till now, it continues to be queried, as the found injured mitochondria might have initiated from neuron-associated astrocytes instead of neurons [101, 102]. Conversely, it was validated that free fatty acids (FFA)generated in the breakdown of neuronal mitochondria possess the capacity of getting transferred in ApoE+ (apolipoprotein E) lipid complexes to astrocytes, where the astrocyte mitochondrial β-oxidation pathway possesses the capability of metabolizing them [103] (Figure 3).

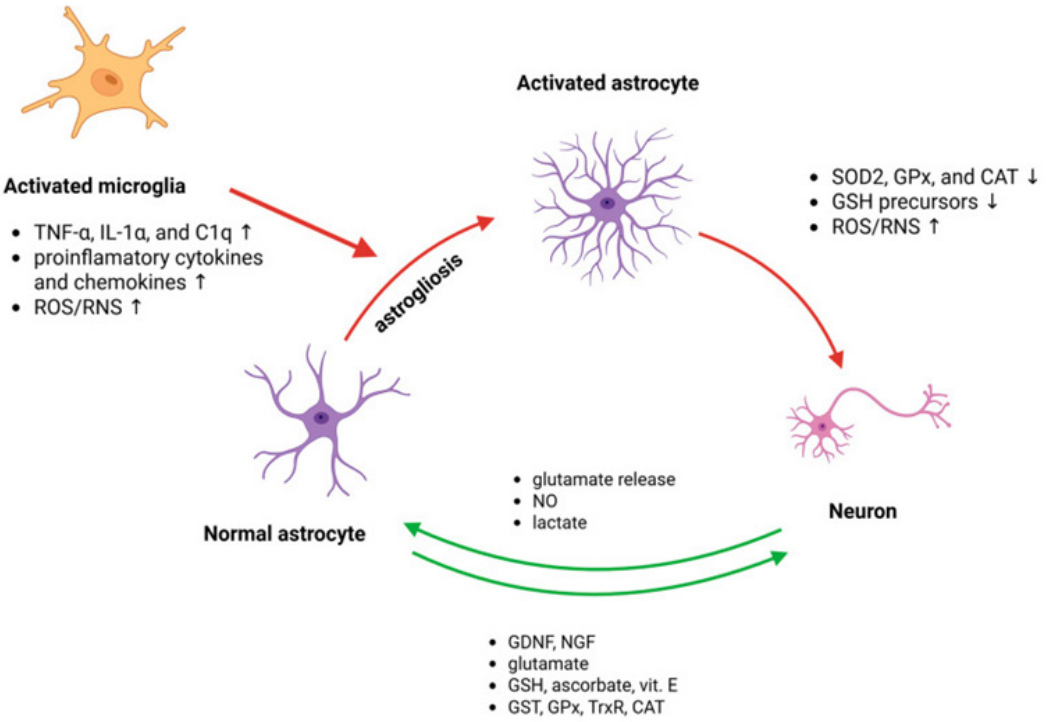

Figure 3: Courtesy ref no-44 - The primary molecular mechanistic modes implicate reactions as well as cross-talk among astrocytes,microglia, in addition to neurons. In case of physiological situations (green arrows), astrocytes sustain homeostasis by i) liberating antioxidants, ii) leading to degradation of ROS/RNS, iii) supplying energy, along with iii) absorbing as well as iii) metabolizing neurotransmitters. In pathological states (red arrows), astrocytes possess the capacity of getting induced by signals from i) activated microglia in addition to ii) activated astrocytes, resulting in i) exacerbated liberation of free radicals as well as proinflammatory cytokines, ii) glial scar generation al, in addition to iii) disturbed controlling of excitatory aminoacids, therefore escalating inimicality of neurological damage.

Neuronal Signals which are Capable of Buttressing Astrocytic Antioxidant Defences

Neuronal signals possess a pivotal part in buttressing astrocytic antioxidant defences via plethora of pathways [104, 105]. Escalated neuronal activity results in the i) liberation of glutamate ii) as well as other soluble factors which iii) activate the astrocytic Nrf2 pathway via group I metabotropic glutamate receptors along with intracellular Ca2+ signalling [106]. This generates a controlling loop where astrocytic neuroprotective capability matches the quantities of neighbouring synaptic activity. Furthermore, NMDA receptor inducing in astrocytes activates a pholipase C- modulated pathway implicating i) protein kinase Cδ (PKCδ) in addition to ii) cyclin-dependent kinase 5 (Cdk5), which phosphorylates Nrf2 along with facilitates its nuclear translocation, thereby stimulating antioxidant gene expression [75]. Neurons further escalate their own antioxidant defences via synaptic NMDA receptor activity, which buttresses the Trx-Prx system by inactivating the thioredoxin hampering agent (Txnip) as well as upregulating genes which reactivates Prx [107].

Taken together such mechanistic modes guarantee potent antioxidant shielding against OS [20] (Figure 3).

Neurons are unreactive to direct redox alterations via Nrf2 activation. i) Rather, they depend on ii) action - modulated calcium- based pathways to escalate the expression of Nrf2 target genes, iii) despite the lack of Nrf2 activation. iv) Such occurrence takes place via an alternative transcription factor, activator protein 1 (AP-1), that associates synaptic actions activity to neuronal redox pathways. v) Intriguingly, the AP-1acknowledgement region is engraved amongst ARE designs [108, 109]. vi) In case of question of astrocytes, neuronal action working is analogous to actuating a switch via mechanistic modes implicating cAMP/PKA (protein

kinase A)- based CREB (cAMP response element-binding protein) activation, escalating the generation of basically antioxidant molecules, for instance i) GPx3 as well as ii) SOD3, that gets liberated outside the cells. GPx3 in addition to SOD3 possess the capacity of iii) being believed tobe an aspect of a meaningful mechanistic modes of non-cell- independent astrocytic antioxidant embracing for neurons [38,105].

Astrocytic Reaction Pathways to Neuronal Signals

i) Redox-based connection amongst ii) neurons as well as ii) astrocytes iii) is vital for sustenance of cellular homeostasis in the brain. Astrocytes yield imperative i) antioxidant embracing to neurons via the Nrf2 pathway, ii) that controls a considerably greater cohort of antioxidant genes, iii) whereas neurons possess inimical Nrf2 action iv) however remunerate via activity- based antioxidant gene controlling [20]. Such intercellular coupling implicates both i) metabolic as well as ii) working communications i) modulated by gap junctions in addition to ii) hemichannels, a) aiding small molecule diffusion, b) along with neurotransmitter recycling [110]. The i) antioxidant as well as ii) bioenergetic systems a) are intricately coupled amongst such cell kinds, b) with neurons metabolizing glucose via the PPP to sustain diminished GSH, based on energy substrate supply from astrocytes [96].

Such neuron–astrocyte interaction guarantees brain bioenergetic in addition to redox homeostasis in health [111] (Figure 3).

i) Astrocytes react to neuronal signals ii) via plethora of unique pathways, iii) enabling
bidirectional connection in the brain. i) Once neurons liberate neurotransmitters,
ii) astrocytes possess the capability of determining such signals as well as iii) reacting with intracellular calcium escalations([Ca2+] i) [112, 113]. iv) Such calcium reactions possess the capacity of continuing to possess placement to particular astrocytic events v) or progressin the form of waves a) right through the cell b) in addition to adjacent astrocytes [113].
Utilization of i) glutamatergic along with ii) nitric oxide- modulated signalling pathways to sense neuronal action takes place via astrocytes [112]. iii) In reaction, astrocytes possess the capacity of liberating glutamate in a calcium- based fashion, iv) that subsequently signals back to neurons a) via NMDA receptors, generating a feedback loop [113,114]. i) Such neuron–astrocyte connection possesses the capacity of ii) influencing variable brain working, iii) controlling inclusive of a) synaptic transmission as well as b) vascular controlling c) via touching of astrocytic with cerebral arterioles [113]. Furthermore, astrocytes i) undergo reactive astrogliosis in pathological situations, ii) involving molecular in addition to iii) morphological alterations iv) that are capable of possessing a) both advantageous, along with b) inimical actions [115] (Figure 3).

Pathological Setting of Neuron–Glial Redox Signalling

Pathological settings of neuron–glial redox signalling i)) implicate complicated cross-talk a) amongst OS as well as b) neuroinflammation ii) which accounts for neurodegeneration. i) In case of normal situations, redox signalling yields imperative cellular connection a) via transient free radicals in addition to b) redox sensors in i) enzymes, ii) receptors,along with iii) transcription factors [116, 117]. Nevertheless, on escalation of OS, the efficacious diminishing potential of redox pairs decreases, switching cell signalling toward proinflammatory as well as proapoptotic pathways, creating a vicious cycle amongst OS in addition to, neuroinflammation [116].

Such pathological redox signalling presents itself at the time of along with subsequent to CNS damages, for instance i) TBI, ii) stroke, in addition to accounts for major neurodegenerative diseases (NDD) inclusive of i) AD,ii) PD, iii) Huntington's disease (HD), along with iv) ALS [117]. Interaction amongst i) proinflammatory as well as ii) oxidative signals result in neuronal injury through concomitant toxic pathways [118, 119]. In prion diseases, changed redox balance promotes i) protein misfolding along with ii) assemblage n, stimulating iii) microglial activation as well as iv) further redox stress [120]. CNS damages, inclusive of i) traumatic damage, ii) stroke, or iii) ND damage, are associated with i) cell demise, ii) inflammation, in addition to iii) OS.

Neuron–Glial Redox Signalling Changes

Alterations in neuron–glial redox signalling i) subsequent to central nervous system (CNS) damage ii) implicate complicated crosstalk amongst i) OS as well

as ii) neuroinflammation, iii) that pivotally shape neurological results. Oxidative pressures change molecular working through i) redox-sensitive enzymes, ii) receptors, in addition to iii) transcription factors, with thiol-based sensors a) that possess specifically susceptibility to oxidative manipulation [116]. i) Once escalation of OS takes place, ii) the reduction potential of redox pairs decreases, iii) switching signalling toward a) proinflammatory along with b) proapoptotic pathways as well as a) buttressing amongst OS in addition to b) inflammation [116].
2)CNS damage starts a graded neuroglial activation programme surrounding i) neurons,ii) glia, as well as iii) endothelia, that is evolutionarily perpetuated for i) conferring protection in addition to ii) healing [121].

Nevertheless, exacerbated interactions amongst i) oxidative, along with ii) proinflammatory signals results in a) neuronal injury along with b) neurodegeneration [118]. C)Decontrolling of redox homeostasis, an elemental facet of i) CNS generation, ii) working, as well as iii) ageing, allow for pathological results [119]. D)Pathological series subsequent to CNS damage are inclusive of i) OS, ii) neuroinflammation,iii) mitochondrial impairment, as well as iv) neuronal apoptosis [122]. The liberation of cytokines for instance i) TNF-α (tumour necrosis factor alpha), ii) IL-1β, in addition to iii) IL-6 augments i) neuronal damage, along with i) dysfunctional regeneration, while anti-inflammatory cytokines, are inclusive of i) IL-10, ii) IL-4, in addition to iii) IL-33, evoke protection conferring actions [123].

The Nrf2 pathway is a central controller of i) antioxidant defence as well as ii) inflammation regulation in acute CNS damage. 1)In TBI in addition to 2) ischemic stroke, Nrf2 activation restricts a) NF-κB(nuclear factor kappa B)– guided proinflammatory reactions, b) diminishing liberation of cytokines for instance ii) TNF-α, ii) IL-1β, as well as iii) IL-6 (interleukin 1β, 6) [124]. 3)In SCI, Nrf2 activation i) circumvents ROS in addition to ii) cytokine synthesis via a) NF-κB interactions [125]. iii) Nrf2 stimulates the expression of iv) antioxidant along with v) detoxifying genes, inclusive of i) HO-1, ii) NQO1, along with iii) enzymes which embrace GSH production [126,127]. Astrocytes possess a pivotal part in 2) ischemic stroke, owing to they illustrate cell particular Nrf2 action pivotal for neuronal survival [128]. 1)Nrf2 deficiency i) escalates NF-κB activation as well as ii) postpones motor/cognitive rectification subsequent to TBI [124,129,130]. Thus, Nrf2 signalling i) confers protection against oxidative injury in addition to ii) inflammation in both a) acute damages, along with b) chronic neurodegeneration, that enables it tobe actingf in the form of an attractive therapeutic target [76,131].

II)One additional pathological mechanistic modes which takes place subsequent to CNS trauma i) implicates reactivation of microglia. Astrocyte activation takes place via complicated molecular mechanistic modes ii) implicating interchangeable connection with microglia. iii) Activation of microglia takes place a) prior to in contrast to b) astrocytes as well as iii) promote astrocytic activation, iv) whereas activated astrocytes possess the capacity of both facilitating a) activation of microglia localized in far off sites in addition to b) hampering local microglial activities [132]. Activated microglia stimulate astrocytes via the liberation of i) TNF-α, ii) IL-1α, iii) C1q (complement constituent1q), iv) that facilitate astrocytes toward the A1 phenotype. A) A1 astrocytes downregulate antioxidant enzymes, for instance i) SOD2, ii) GPx, along with iii) CAT, a) therefore reducing their capability of providing neurons with GSH precursors as well as b) escalating oxidative damage [133]. B) Extra molecules i)implicated in astrocyte activation are inclusive of ii) vital compounds like i) ATP, ii) controlling hormones for instance i) gonadal steroids, in addition to ii) injury- stimulated a) cytokines , along with b) chemokines [134].III) Such interdependent cross-talk amongst microglia as well as astrocytes guides reactive gliosis, i) resulting in glial scar generation which i) identifies injured sites ii) however possess the capacity of further hindering axonal regeneration [135,136].

C)The third setting resulting in diminished antioxidative reactions in neuron–glial cross-talk implicates i) excitotoxic glutamate along with ii) redox dysequilibrium. I)Excitotoxic glutamate-redox dysequilibrium i) delineates a pivotal pathological mechanistic mode ii) subsequent to CNS damage, iii) implicating complicated crosstalk amongst a) glutamate signalling in addition to b) OS. Microglia allow for excitotoxicity iv) via the glutamate/cystine antiporter system xc−, a) that controls both glutamate liberation liberation as well as b) cellular redox equilibrium, c) with greater

GSH:GSSG ratios anticipating neurotoxic potential [rev by us in 35-37,137]. II)TBI i) disturbs normal glutamate in addition to ii) GABA homeostasis, iii) generating excitation- hampering dysequilibriums that evolve via i) acute, ii) subacute, along with iii) chronic phases [138]. The redox biology of excitotoxicity i) implicates NMDA receptor manipulation, ii) the oxidative transformation of DOPA to the neurotoxic TOPA quinone, iii) in addition to the secretion of zinc from intracellular proteins, correlating i) glutamate neurotoxicity to ii) oxidative cellular series [139].

The sequelae of CNS damage further possess the capacity of the secretion of damage-associated molecularpatterns (DAMPs) from injured neurons [140]. Neuronal DAMPs possess a pivotal part in activating astrocyte- modulated reactions that possess the capacity of aggravating neurodegeneration.

Chang et al. [141], illustrated in 2024that factors released from demising neurons signal via i) the receptor for advanced glycation end-products (RAGE) to activate ii) astrocytic RIPK3 (receptor-interacting serine/threonine-protein kinase 3) signalling, facilitating neuroinflammation as well as further dopaminergic cell demise in PD models [141]. This generates a destructive cycle where neuronal demise perpetuates extra neurodegeneration via inflammatory astrocyte activation. The OS constituent implicates complicated cross-talk amongst neurons, along with astrocytes. Reyes et al. [142], in 2012 illustrated that NMDA receptor activation in neurons stimulates the liberation of extracellular superoxide through NOX2 (NADPH oxidase 2), leading to OS in adjacent neurons in addition to astrocytes [142]. Nevertheless, astrocytes further possess the capacity of offering protection conferring actions to neurons by controlling oxidative signalling in a controlled manner. Haskew-Layton et al. [143], in 2010 observed that lesser -amount hydrogen peroxide generation in astrocytes protection conferring neurons from OS via Nrf2 autonomous - pathways, whereas greater amounts assumed neurotoxicity, stressing the double part of astrocytic oxidative reactions [143].

In CNS damages like i) stroke as well as ii) TBI, the iron accrual results in significant brain injury by facilitating OS in addition to stimulating a kind of cell demise referred toas ferroptosis. Ferroptosis, an iron- based programmed cell demise, possesses a pivotal part in pathogenesis of CNS damage via i) interference with iron metabolism, ii) GSH elimination, in addition to iii) lipid peroxidation [144]. i) Iron modulated - ROS production, in astrocytes delineates a pivotal mechanistic mode in neurodegeneration, along with ii) OS. iii) Astrocytes demonstrate sensitivity to acute iron overburden, i) with iron entry leading to dysfunctional cellular reducing potential as well as ii) facilitating ROS generation, iii) eventually causing cell demise via iv) mitochondrial impairment [145].

Accrual of iron in cultured astrocytes takes place i) in a time- as well as ii) quantity - based fashion iii), eventually leading to transient escalation of intracellular ROS in addition to mild cytotoxicity. Nevertheless, astrocytes possess adaptive mechanistic modes, inclusive of i) upregulation of ferritin, along with ii) manipulation of transferrin receptor quantities to manage iron homeostasis [146]. Despite iron oxide nanoparticles i) stimulate transient ROS generation as well as ii) ferritin upregulation, even once though astrocytes continue to be viable although there are escalated iron levels [147]. Noticeably, astrocytes illustrated higher resistance to OS- in contrast to oligodendroglia, owing to their escalated GSH quantities in addition to lesser iron quantities, that enables them to less vulnerability to ROS-modulated damage [148]. Astrocytes act in the form of vital controllers of brain iron metabolism, efficaciously resulting in accrual iron ions as well as iron-possesing compounds via particular transport proteins whereas storing iron in ferritin to confer protection against toxicity [149].A) In case of normal situations, i) astrocytes possesses the capability of robust iron transport , along with ii) are located adjacent to blood vessels, iii) that enables them in the form of vital governers of brain iron homeostasis iv) despite possessing lesser metabolic iron needs in contrast to oligodendrocytes [150]. In NDD's, astrocytes i) primary targets of iron neurotoxicity, ii) resulting in deficiencies iii) in the glutamate/GABA-glutamine shuttle, iv) the antioxidative machinery, as well as iv) energy metabolism which promote neurodegeneration [151]. Iron accrual takes place over variable neurological situations, inclusive of i) PD, ii) AD, in addition to iii) SCI, owing to decontrolled iron homeostasis mechanistic modes. Recent advances have emphasized ferroptosis in the form of a vital iron- based cell demise pathway in the lipid-rich CNS milieu [152]. I)Subsequent to

ischemic stroke, i) glial cells illustrate ii) attractive therapeutic targets in view of their iii) implication in iron transfer amongst a) glia, along with b) neurons, c) implying plethora of key glia-neuron crosstalk in modulating ferroptosis- associated pathology [153]. Ferroptosis influences plethora of CNS cell kinds, illustrate greater inclusive of i) glial cells, ii) neurons, as well as iii) pericytes, with a) iron overburden in addition to b) accrual of lipid reactive oxygen species (ROS) which accounts for neuronal damage [154].

i) The NF-κB , along with ii) JAK/STAT (Janus kinase/signal transducer and activator of transcription) signalling pathways possess a pivotal part in facilitating a) neuroinflammation in astrocytes, b) specifically II) subsequent to SCI, once they c) originate gene expression correlated with i) astrogliosis as well as the ii) generation of proinflammatory factors. Such pathways are reciprocally connected, in view of i) NF-κB activation results in the a) liberation of IL-6, that in turn ii) b) activates STAT3 signalling [155]. reciprocal the predominance of proinflammatory signalling) ii) across antioxidative reactions iii) implicates complicated molecular interactions amongst a) NF-κB in addition to b) Nrf2 pathways [156]. i) Nrf2 , along with ii) NF-κB are transcription factors that control a) antioxidant as well as b) inflammatory pathways in reverse fashions [139]. iii) In the lack of Nrf2 a), predominant NF-κB activity results in i) escalated cytokine generation [156].

III)Astrocytes possess a pivotal part in neurological rectification subsequent to CNS damage by coupling their metabolism with that of neurons. A) In case of normal situations, i) astrocytes utilize glycolysis, ii) whereas neurons depend on oxidative metabolism. Astrocytes yield metabolites, for instance i) lactate as well as ii) amino acid precursors, iii) to embrace neuronal energy requirements in addition to iv) sustain redox harmony [157]. B) Subsequent to TBI, i) such metabolic collaboration is disturbed, ii) with glucose oxidative metabolism being more robustly dysfunctional in neurons iii) in contrast to in astrocytes [158]. Astrocytes react to TBI with i) reactive astrogliosis, ii) possess the features of changes in gene expression, iii) morphology, iv) specifically as well as v) working that possess the capacity of vi) either facilitating a) neural healing b) or allow for secondary damage [159]. Vital astrocyte working that influence neuronal survival are inclusive of i) glutamate uptake, ii) free radical searching, in addition to iii) cytokine generation. B) Their accounting for long-term rectification implicates b) the utilization of liberation of trophic factors, for instance i) NGF, ii) bFGF (basic fibroblast growth factor), iii) TGFβ (transforming growth factor beta), ivPDGF (platelet-derived growth factor), v) BDNF (brain-derived neurotrophic factor), and) vi) CNTF (ciliary neurotrophic factor), embracing for synaptic redistribution organization [160]. B.Pathological neuron–glial interaction subsequent to CNS injury ii cause inimicality of astrocytes' antioxidant defences i) by hampering the Nrf2 pathway. i) This promotes neurotoxic cell behaviours, ii) disturbs glutamate as well as iii) metabolic interactions, iv) dysfunctional mitochondrial working, v) in addition to v) results in continuing inflammation. This generates a feed-forward cycle i) implicating OS, ii) neurodegeneration, along with iii) glial impairment.

Neuron–Glia Redox Signalling in CNS Damages

TBI is associated with i) escalated inflammation as well as the ii) production of considerably oxidative situations, which are implicated in the so-labelled secondary strike action [161–163]. i) The extensive production of ROS damage ii) disturbs astrocyte working in addition to iii) influence neuron– glia cross-talks. In the brain biopsies of brain injury patients, iv) a diminished expression of astrocytic glutamate transporters (EAATs) has been observed. Such finding implicates a diminished capability of astrocytes to pick up excitatory amino acids [164]. i) The accrual of excitatory amino acids in the micromilieu possess the capacity of resulting in ii) mitochondrial calcium overburden, iii) intensifying OS as well as iv) neuronal damage. i) The antioxidative potential in addition to ii) diminished generation of ROS subsequent to mechanical damage iii) are capable of rectification of in addition to an iv) escalation of hydrogen sulphide- possessing (H2S) molecules, v) therefore reducing the secondary strike actions. vi) Such protection conferring results takes place due to glutamate transporter (GLT-1) expression stimulation [165]. Mechanical stresses correlated with brain damage might stimulate a mitochondrial malfunction series in astrocytes, that subsequently spreads to neurons [166]. Stroke is one of the main causes of disability or demise globally. It is a clinical condition characterized by insufficient blood flow in the CNS. It possesses the capacity of stemming a result of both i) hemorrhage or ii) ischemia

[167]. i) At the time of as well as ii) subsequent to the stroke incident, cell damage takes place basically due to the escalated OS. ii) Astrocytes, in the form of vital actors in the antioxidative reaction in the CNS, possesses a) a double part at the time of stroke in addition to b) rectification. They possess the capacity of getting involved in both a) neuroprotection as well as b) neurotoxicity, based on their reaction to the micromilieu situations stimulated by stroke. In forebrain ischemia, an overexpression of astrocytic-particular SOD2 confers protection to neurons from ischemia- associated injury [168]. II) Furthermore, in cerebral ischemia, astrocytes are capable of a) directly or b) indirectly switching their working mitochondria to neurons. B)Barricading of such switching possess the capacity of efficaciously reducing neuronal damage which occurs from cerebral ischaemia [81]. Stroke stimulated escalation of OS i) triggers astrocyte activation, that, in turn, ii) accounts for dysfunctional neurological rectification iii) by creating glial scars [169,170]. i) Oxygen–glucose dissipation stroke influences ii) the expression, iii) organization, in addition to iv) action of glial glutamate transporters. v) This results in dysfunctional cellular glutamate uptake, along with diminished intracellular GSH quantities, the manner corroborated in vitro in differentiated astrocytes [171].

Neurodegenerative- Associated Neuron–Glial Redox Signalling

i) the amyloid series posit of AD, the generation of amyloid β (Aβ) is associated with an escalated susceptibility of brain tissue to oxidative signals [172]. ii) Aβ liberated into the extracellular space iii) possesses the tendency to oligomerize, that, in turn, iv) cause dysfunctional NMDA receptor activity, v) resulting in the production of extracellular ROS in addition to vi) aggravate calcium influx into neurons, vii) ultimately leading to mitochondrial impairment [173–175]. Additionally, a) Aβ agglomerates into fibres along with b) aged plaques, whose generation i) escalates the OS as well as ii) facilitates apoptosis [176]. Post-mortem evaluation of the brains of AD patients documented that Nrf2 is i) pronouncedly expressed in the cytoplasm in hippocampal neurons, in addition to, ii) it does not get copositioned with beta amyloid a) plaques or b) neurofibrillary tangles. iii) Additionally, the expression of Nrf2 in the nucleus is meaningfully diminished. Such outcomes point that Nrf2- guided transcription a) does not get activated in neurons at the time of AD, b) despite the existence of OS [177]. Conversely, recent studies evaluating post-mortem AD brain tissue have illustrated a) escalated quantities of Nrf2 as well as b) p62 in cells with i) greater amyloid precursor protein or ii) neurofibrillary tangles. Furthermore, other Nrf2 targets as well as their gene transcripts are further escalated [60,178,179]. B) In reference to astrocytic Nrf2 expression in AD, Nrf2 apparently gets expressed in the nucleus of certain hippocampal astrocytes [177]. The evaluation of Nrf2-targeted genes in astrocytes has illustrated escalated NQO1 quantities i) in hippocampal in addition to ii) frontal cortex neurons in AD brains [180–182]. iii) A considerable escalation in NQO1 quantities is in astrocytes encompassing plaques in both sites [181,182]. HO1 quantities are escalated in i) neurons as well as ii) astrocytes amongst the a) temporal cortex in addition to b) hippocampus [183–185], along with in iii) microglia in the hippocampus of brains impacted by AD. HO1 is further observed in i) astrocytes as well as ii) microglia reacting to mutated tau expression in the hippocampus of mice [178]. In variable human pathologies, i) meaningful changes in astrocytic working in addition to ii) morphology are found. In the literature, the abovementioned alterations are labelled as reactive astrogliosis. Events which stimulate i) reactive astrocytes surround inflammatory signals, ii) elimination of neuronal touch, at the time of the direct sequelae of disease-associated proteinopathy [133,186,187]. The enrichment of reactive astrocytes is observed]. i) in AD brain tissue, ii especially in Aβ or tau-enriched site [188–190]. Furthermore, astrocytes might be induced by microglia activation to biogenerate i) inflammatory factors, ii) NO, as well as iii) ROS, taken together compounds which actually facilitate a redox status dysequilibrium [191]. In AD patients' brains, astrocytic i) GSH liberation in addition to ii) GSH- generating enzymes, for instance GCL, are further decontrolled. At the initial stages of AD, i) monomers of Aβ (mAβ) stimulate GSH liberation, ii) thus escalating astrocyte- associated antioxidant potential. Once Aβ agglomerates,it causes escalation in the form of i) oligomers, ii) fibrils, or iii) amyloid plaques, the astrocytic machinery that embrace GSH liberation, specifically through ABCC1, assumes dysfunctionality. This diminishes the neural milieu's antioxidant buffering capacity. In effect, i) extracellular GSH liberation reduces, ii) plausibly aiding in escalated oxidative damage once the disease propagates [192].

I) PD is categorized in the form of the second maximum frequent NDD subsequent to II) AD,along with the commonest etiological factor of movement associated conditions - throughout world [193]. i) The pathogenesis of PD is associated with α-synuclein (α-Syn) accrual in neurons. In the PD model, it was collaborated that α-Syn possesses the capability of getting transferred from neurons to astrocytes, ii) where it induces a robust reaction iii) resulting in astrocyte as well as microglia activation [194–197]. Additionally, α-Syn stimulates astrocytes to i) aggravation of ROS generation as well as ii) proinflammatory cytokines through iii) TLR4 receptors, owing to which it was illustrated in an in vitro model [198]. iv) Furthermore, the accrual of αSyn might escalate the inimicality of OS in astrocyte-neuron co-culture systems, resulting in a) lipid peroxidation in addition to b) neuronal demise [199,200].

III)The next NDD generating owing to redox dysequilibrium is ALS. i) In its familial form, roughly 90% of patients are carriers of the SOD1 mutation [201]. ii) Studies utilizing a) mutant SOD1 in murine models, along with b) in vitro culture systems indicate that astrocytes possess a pivotal part i) in progressing motoneuron damage in addition to ii) disease progression [202, 203]. iii) Astrocytes overexpressing the mutated SOD1 gene liberated a) escalated quantities of TGFβ, along with b) inflammasome NLRP3. c) They also illustrated an escalated activation of the NF-κB pathway, d) therefore resulting in aggravation of the inflammatory reaction in the model system [201].

Therapeutic Plausibility

Astrocytes, a basic ingredient in sustenance of redox homeostasis in the brain, have assumed a greater concentration in the form of plausible targets for arbitration subsequent to CNS damages. Plausible settings of modulating targeting astrocyte redox dysequilibrium are inclusive of variable modalities, for instance i) the utilization of small-molecule Nrf2 activators, ii) renewal of GSH/thiol pools, iii) MTAs (mitochondria-targeted antioxidants) simulating agents, iv) manipulation of astrocyte reactive phenotype, v) administration of antioxidant enzymes/catalytic rummagers through biologics/nanodelivery, vi) hampering of astrocyte- associated ROS facilities, vii) extracellular vesicles treatment to administer antioxidant cargo, or vii) RNA/gene arbitrations. i) The initial approach implicates activation of astrocytic Nrf2. Astrocytic Nrf2 activation robustly escalates local antioxidant capability as well as confers protection to adjacent neurons. ii) Therefore, utilization of small-molecule activators possesses the capacity of getting believed tobe a plausible strategy for Nrf2- associated antioxidative reactions in astrocytes. Uptill now, a broad plethora of molecules have been isolated in the form of Nrf2 activators, amongst whom certain are of plausible clinical attraction, owing to which they possess the capacity of efficaciously triggering an antioxidative programme through the Nrf2-ARE pathway.

Nrf2 Activators

I) i) Tert-butylhydroquinone (tBHQ) in addition to, ii) sulforaphane were amongst the initial agents assessed for plausible employment In decreasing OS accrual to the least . Scientific investigators work illustrates that i) tBHQ along with ii) sulforaphane illustrate meaningful therapeutic plausibility in tackling redox dysequilibriums in astrocytes. Such two agents serve in the form of an activator of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, whose predilection takes place in astrocytes as well as yields neuroprotection [204]. Subsequent to TBI, tBHQ therapy efficaciously decreases astrocyte overactivation ii) whereas escalating Nrf2 nuclear accrual as well as iii) upregulating downstream antioxidative genes encoding a) HO-1 in addition to b) NADPH-quinone oxidoreductase-1 [205]. The substance meaningfully i) ameliorates OS markers, ii) decreases malondialdehyde quantities, iii) escalates superoxide dismutase (SOD), actions, along with iv) reduces brain edema in mice subsequent to TBI [206]. v) Additionally, tBHQ illustrates anti-inflammatory characteristics by a) decreasing NF-κB activation as well as b) diminishing proinflammatory cytokines, inclusive of i) TNF-α, ii) IL-1β, in addition to iii) IL-6 [207]. v) Such observations overall advocate i) tBHQ , along with ii) sulforaphane as attractive therapeutic substances for managing astrocyte- modulated redox dysequilibrium in CNS damages. Nevertheless, in the case of tBHQ, a frequently utilized food preservative, it results in avoidance of the oxidation of unsaturated fats. As per certain documents, the long-term exposure to TBHQ at greater dosages (0.7 mg/kg) leads to a cascade of inimical sequelae, inclusive of i) cytotoxic, ii) genotoxic, iii) carcinogenic, along with iv) mutagenic actions [208]. Correspondingly, to tBHQ, sulforaphane

i) activates the Nrf2 pathway, ii) therefore decreasing the risk of OS in an in vitro model of ischemia/reperfusion, on iii) implementation both in the form of iv)) pre- in addition to v) post- therapy subsequent to the damage [209,210] .

Although, attractive initial outcomes from preclinical studies, plethora of botherations restrict the practical conduciveness of concentrated antioxidative therapies. A main hurdle is crossing BBB, which limits the accessibility of several small molecules. For example, the capability of tBHQ as well as sulforaphane in penetrating the BBB differs meaningfully. Ii)Sulforaphane illustrates detectable brain entry in mice, its accrual takes place swiftly in the ventral midbrain in addition to striatum 15 min subsequent to systemic delivery, followed by attaining basal quantities amongst 2 h, the manner evaluated by HPLC [211]. Such short however measurable existence takes place parallel with upregulation of Nrf2- based genes in brain microvessels, along with tissue, suggesting it possesses the capability of working directly amongst the CNS whereas guaranteeing sustenance of BBB wholeness. On the other hand, corroboration for tBHQ crossing the BBB is restricted as well as usually indirect [212]. tBHQ has exhibited neuroprotective actions in models of i) subarachnoid hemorrhage in addition to ii) TBI, both implicating BBB agreement, however there is no quantitative pharmacokinetic outcomes corroborating its gaining entry into brain in case of the normal situations. Certain studies further point that pre-ischemic exposure to tBHQ possess the capacity of BBB disturbance, along with OS in endothelial cells, indicating that vascular actions might be based on the background. Taken together, such observations point that whereas sulforaphane possesses the capability of probably achieving efficacious CNS quantities, tBHQ's central actions might be based on the BBB injury or secondary systemic mechanistic modes [213]. A greater insight of i) ii) their transport, iii) organization amongst the brain plasma, iv) long-term vascular actions is imperative prior to either their possessing the capacity of getting generated safely in the form of therapeutic Nrf2 activators [214, 215].

B)Omaveloxolone, an innovative Nrf2 activator, demonstrates attractiveness in the form of a therapeutic arbitration subsequent to CNS damage via several mechanistic modes. In intracerebral hemorrhage models, omaveloxolone promoted i) Nrf2 nuclear accrual, ii) escalated the expression of antioxidant enzymes, for instance a) HO-1 as well as b) NQO1, in addition to iii) modulated microglial polarization from proinflammatory M1 to anti-inflammatory M2 phenotypes, iv) whereas improvements in sensorimotor working [216]. v) The substances further illustrated effectiveness in Friedreich's ataxia models by a) rectification of effectiveness of mitochondrial Complex I action, b) diminishing OS markers, inclusive of c) lipid peroxidation as well as d) mitochondrial ROS, in addition to e) protection conferring against mitochondrial depolarization [217]. i) Omaveloxolone illustratesd the capability of crossing BBB, along with ii) attained estimatable brain quantities in preclinical studies. Specifically, in monkey studies, oral delivery of omaveloxolone ledto determinable, dose based - quantities in i) brain tissue as well as in the ii) lungs in addition to iii) liver. Omeveloxolone illustrated i) dose-linear plasma pharmacokinetics, along with ii) dose- based stimulation of Nrf2 target genes, iii) inclusive of in brain tissue, ii) once evaluated in the form of plausible agents iv) in reference to therapy of neurological disorders for instance Friedreich's ataxia [218]. Nevertheless,the conduciveness omeveloxolone, in the form of an innovative agent targeting OS subsequent to CNS injury, needs greater asssessment.

C)Ginsenosides, the primary bioactive constituents of ginseng, delineate one additional intriguing group of compounds [219]. Among all the ginsenosides possessing natural existence in ginseng, the delivery of ginsenoside Rh1 (protopanaxatriol) possess the capacity of i) efficaciously hampering the production of hydrogen peroxide-related ROS, ii) therefore escalating the cell viability of rat primary astrocytes. Studies in reference to mechanistic modes, pointed that Rh1 therapy enrolled a) Nrf2 as well as b) c-Jun to ARE sequences in addition to, c) sequentially, triggered the expression of phase II antioxidant enzymes, inclusive of i) HO-1, ii) NQO1, iii) SOD2, along with iv) CAT [220]. B) The antioxidative action is further found with ginsenoside Rg1, that confers protection against ischemic/reperfusion- stimulated neuronal damage through the miR-144/Nrf2/ARE pathway. miR-144 downregulates Nrf2 expression by targeting its 3 ′ -untranslated area in PC12 cells cultured under oxygen–glucose dissipation situations. Additionally, delivering Rg1 (20 mg/kg) to tMCAO rats meaningfully diminished

ischemic damage by activating the Nrf2/ARE pathway [221].

Cii)The manner illustrated in the in vitro model, the combination of i) ginsenoside Rb1, ii) ginsenoside Rg1, iii) schizandrin, in addition to iv) DT-13 (saponin compound from Liriope muscari), substances obtained from the Chinese canonical medicine formula ShengMai preparations, v) controls the Nrf2/HO-1 pathway in treated PC12 cells undergoing H2O2-therapy [222].

Ginsenosides possess considerably restricted capability of crossing the BBB, with maximum research illustrating ed inimical transport. Specifically, only Rg1 was detected in brain tissue subsequent to oral consumption as well as despite, that in just miniscule trace levels [223]. Further studies confirmed this, noting that Rg1′ s passage via the BBB is limited considerably as well as usually undetectable in both normal in addition to ischemic rat models [224]. Furthermore, ginsenosides undergo extensive metabolic alterations in the a) gastrointestinal tract (GIT), along with b) liver, which probably further diminishes their BBB permeability [225]. Whereas, ginsenosides possess attractiveness in reference to pharmacological probability, their direct gaining entry into the brain continues to be considerably restricted.

B) One additional plausible therapeutic strategy is the direct metabolic embracing in reference to renewal of the GSH pool in the CNS, particularly in astrocytes. Delivery of cysteine precursors, for instance N-acetylcysteine (NAC), possess the capacity of allowing sustenance of diminished GSH amounts [226,227]. In reference to TBI, variety of preclinical studies in rats have illustrated that NAC therapy i) diminishes markers of OS, ii) attenuates blast- associated changes in BBB in addition to iii) approach wholeness, along with iv) causes improvement of cognitive working subsequent to regulated cortical influence or blast damage [228–230]. NAC therapy subsequent to TBI induces the antioxidative programme through the Nrf2-ARE pathway [231]. The proof-of-concept pilot study “Pro-NAC” (ClinicalTrials.gov NCT01322009), that delivered a combination of probenecid in addition to NAC to children with robust TBI, has illustrated attractive outcomes that possessed the capability of being embraced in the future in reference to creating a pharmacological approach for TBI therapy. Probenecid, utilized in the form of an adjuvant in this study, is a well- acknowledged hampering agent of ATP-binding cassette as well as solute carrier transporters, that causes avoidance of the transport of organic acids, for instance NAC [232]. Further, a double-blind, randomized controlled study implicating 81 patients illustrated that NAC supplementation turned out to be advantageous in the persons that had exposure to blast- stimulated mild TBI. The study emphasized improvements in neuropsychological investigations, diminished TBI symptoms, as well as swifter rectification time period in contrast to placebo.

Pharmacokinetic outcomes illustrate that oral delivery of NAC possesses considerably inimical bioavailability, varying from 4% to 9% [233]. Despite scientific investigators research indicates that NAC possessed the capability of crossing the BBB [234]. Once delivered orally at dosages up to 70 mg/kg, NAC attains cerebrospinal fluid (CSF) quantities of about 9.26 □} 1.62 μM, with no meaningful inimical sequelae, in addition to is well tolerated by persons [235].

Apparently GSH delivery represents an easiest approach for escalating antioxidant plausibility in the central nervous system (CNS), subsequent to damage. Nevertheless, GSH administration is bothersome owing to its lesser bioavailability as well as inimical stability, particularly in brain tissue.

Innovative administration methodologies with utility of nanomaterials in addition to liposomes illustrate attractiveness improvements in therapeutic effectiveness [236,237]. Greater exhaustive methodologies are inclusive of escalating cysteine uptake by upregulating the xc− system (cystine/glutamate antiporter), escalating GSH generation through transcriptional factors for instance Nrf 2, along with ATF4 (activating transcription factor4 [238]. The upregulation of the xc− system in astrocytes mirrors an attractive however complicated plausible therapeutic strategy for CNS injury, with corroboration pointing to both protective as well as plausibly inimical mechanistic modes. The xc− system transporter vitally modulates cystine/glutamate exchange, that is imperative for GSH generation in addition to conferring oxidative protection [239]. IL-1β has been documented to upregulate system xc− activity in primary mouse astrocytes,

escalating cystine uptake [240–242].

III)Mitochondria-targeted antioxidants (MTAs) illustrated meaningful therapeutic potential for CNS damages by tackling OS as well as mitochondrial impairment in both neurons in addition to astrocytes. MTAs delineate synthetically modulated antioxidant molecules fashioned particularly in reference to their accrual in mitochondria. Various studies with utilization of mouse models of TBIor SCI have documented the effectivenessof MTAs, for instance Mito-Q (mitoquinone—ubiquinone derivative), SS-31 (elamipretide), as well as sinomenine, in escalating neuroprotection by modulating astrocytic antioxidative potential. Such antioxidants efficaciously cause avoidance of cardiolipin oxidation, decrease neuronal demise, along with diminish behavioural deficiencies in addition to cortical disfigurement volume [243–248].

The literature outcomes indicate that SS-31 along with Mito-Q possessed the capability of efficaciously crossing the BBB as well as targeting mitochondria. Nevertheless, Mito-Q coaccrual in mitochondria needs it to get conjugated to a lipophilic triphenylphosphonium cation [249–252]. In a mouse model of TBI, intraperitoneal administration of Mito-Q leads to plethora of -hundred-time accrual amongst mitochondria, therefore eliciting neuroprotective effects [248]. Sinomenine further is capable of passing the BBB once the delivery is done orally or intraperitoneally [253,254]. Oral dosaging of sinomenine led-to 80% bioavailability as well as tissue penetration, inclusive of the brain, amongst 45 min of delivery, pointing benefits in clinical use [253]. Additionally, the administration of sinomenine to astrocytes can be efficaciously escalated by conjugation to hydroxyl-terminated production -4 PAMAM dendrimers, the manner illustrated in a pediatric TBI rabbit model [255]. In ALS, mitochondrial impairment in SOD-1G93A astrocytes facilitates motor neuron degeneration via escalated superoxide production in addition to respiratory defects. MTAs, for instance Mito-Q, along with Mito-CP (mito-carboxy proxyl), at nanomolar amounts efficaciously causes avoidance of such impairment in addition to result in rectification of motor neuron survival [256]. In the rat model of AD, the continued administration of one additional MTA, SkQ1(plastoquinone derivative antioxidant), has illustrated an attractive approach for the avoidance of as well as therapy of AD, possesses the properties of a normalized gene expression profile of astrocytes in addition to, microglia, along with a shift in the resting/activated microglia ratio toward a diminishing in activated cell density [257]. Furthermore, SkQ1 reppressed p38 MAPK signalling pathways as well as illustrated plausibility of avoidance of or gradual disease propagation [258]. SkQ1 illustrates attractive confirmation of BBB penetration in addition to neuroprotective actions in CNS damage models, via direct pharmacokinetic studies are restricted. In the TBI rat model, a single intravenous injection of SkQ1 (250 nmol/kg) showed i) significant neurological advantages, ii) diminishing motor working dysfunction along with iii) resulting in improvement in neuronal survival [259]. The neuroprotective plausibility of MTAs possesses the capability of further getting utilized in HD. Intriguingly, in the fashion mentioned, the synthetic antioxidant XJB-5-131, once delivered to HdhQ150 animals with well- illustrated HD, caused i) improvement in weight gain, ii) caused avoidance of neuronal demise, iii) diminished neuronal oxidative damage, in addition to iv) reppressed the diminishing in motor performance. Histological asssessment furthermore, documented, i) no meaningful variation in gliosis ii) once contrasted to control animals [260].

IV)The maximum advanced arbitration inclusive of astrocyte reprogramming by utilization of i) mRNA (messenger RNA), ii) siRNA (small interfering RNA), as well as iii) miRNA (microRNA). Such strategies illustrate attractive therapeutic plausibility for manipulating redox dysequilibrium subsequent to CNS damage [261–263]. Despite the corroboration continues to be mainly preclinical; the manner shown in aTBI mouse model, i) effective administration plausibility of BDNF mRNA loaded to a novel lipid nanoparticle (DA6LNP), ii) that internalizes to the astrocytes, iii) resulted in overexpression of BDNF in the brain, iv) subsequent to only two repeated intravenous injections. Animals delivered with BDNFmRNA illustrated a meaningful improvement in cognitive capabilities in contrast tothe control group [212]. Particularly, BDNF has been illustrated to reduce reactive oxygen species as well as escalated antioxidant defences in astrocytes by activating Nrf2 [264,265]. One additional strategy regarding manipulating astrocyte working subsequent to CNS damage implicates siRNA- dependent strategies. Particularly, siRNA has been demonstrated to efficaciously target along with downregulate genes

correlated with astrocyte reactivity. Smith et al. [266], have documented in 2018 a proof-ofconcept use of the packaging RNA (pRNA)-derived three-way junction (3WJ) pattern in the form of a stage for delivering siRNAs to downregulate reactivity- correlated genes. In that study,injecting anti-Lcn2-3WJs directly into the disfigurement in mice with SCI was successfull in diminishing Lcn2 amounts at both the mRNA and protein amounts in vivo, thereby reducing astrogliosis [266].

An attractive podium in reference to manipulating the antioxidative plausibility in astrocytes is utility of an astrocyte-targeting peptide (AS1) conjugated to lipid nanoparticles in addition to, encapsulating siRNA targeting the gene of attraction. Such approach has been illustrated in a mouse model of stroke, where an empirical therapy was obtained intravenously to the model animals. Nevertheless, the discussed mediation targeted MEGF10, a vital molecule modulating astrocytic phagocytosis of synapses, that is substantially upregulated at the time of the chronic phase of stroke, resulting in synapse elimination in addition to aggravating brain damage. Although the validated high biocompatibility of the utilization of siMEGF10-LNP@AS1 system, further studies are imperative regarding corroboration of its safety along with the long-term actions of such newly posited astrocyte-targeted administration approach [267].

The manner briefly described, cell reprogramming provides an innovative approach to escalate their antioxidative plausibility for therapeutic mediations subsequent to CNS damage. Apart from the aforementioned administration strategies, the i) installation of antioxidant-encoding transgenes to astrocytes or neurons, for instance ii) Nrf2, possess the capacity of installation getting attained by utilization of viral vectors, inclusive of a) lentivirus or b) adeno-associated virus (AAV) [268–271]. Nevertheless, a problematic botheration is a) that persistent Nrf2 activation in astrocytes subsequent to CNS damage b) faces a plausibly meaningful biological concern even with its well-illustrated neuroprotective actions. Maintained Nrf2 signalling possess the capacity of guiding indelible stimulation of antioxidant as well as detoxifying enzymes, however it might further disturb astrocyte homeostasis via maladaptive metabolic reprogramming in addition to, dysfunctional autophagic flux. Specifically , chronic Nrf2 activation, correlated with p62–Keap1 feedback loops, has been associated with plethora of tissues to i) autophagy impairment, ii)) abnormal cell survival, along with iii) diminished capability of rectification of oxidative damage iv)subsequent to the passage of acute phase [272].II) Furthermore, inherent Nrf2 actions is recognized in cancer biology in the form of a i) promoter of prosurvival, ii) anti-apoptotic phenotypes, iii) escalating theoretical problems that long-term upregulation in reactive astrocytes, i.e iv) cells possesing the capability of proliferation at damage situations a) possess the capacity of heightening pathological gliosis or b) in extravagant settings, a) allow for tumour- facilitating milieus [273,274]. Recognized such risks, astrocyte-targeted Nrf2- dependent treatments need orchestration of the short-term advantages of diminishing OS with mechanistic modes guaranteeing transitory, intricately controlled activation to prevent weakening long-term tissue stability as well as rectification.

Preclinical studies illustrated i)) improved cellular survival, ii) diminished OS markers,
in addition to iii) working rectification) iv) with a) astrocyte-targeted Nrf2 manipulatingor by manipulating of antioxidant genes. Uptill now, such approaches continue to be preclinical, along with no registered human

trials particularly administering antioxidant genes to astrocytes have documented outcomes. It needs further evaluation concentrated on safety, prolonged durable expression, as well as cell particular - targeting before clinical translation. Vital botherations are inclusive of efficacious CNS administration of nucleic acid therapeutics further than the BBB [275]. Whereas attractive as per mechanistic modes, clinical translation continues to be restricted, needing further generation of administering strategies in addition to safety profiles.

Conclusions

Astrocytes are vital for sustenance of redox orchestration in addition to advocating neuronal survival subsequent to CNS damage. Approaches with the objective of rectification of astrocytic redox homeostasis, for instance i) small molecule Nrf2 activators, ii) thiol top-up, as well as iii) MTAs, possess meaningful plausibility in diminishing oxidative in addition to

inflammatory damage. Furthermore, incepting strategies for instance i) astrocyte reprogramming, along with ii) mRNA, iii) miRNA, iv) siRNA, as well as v) gene therapeutics is attractive in reference to for neural healing by manipulating astrocyte working. i) Despite attractive preclinical outcomes, ii) clinical translation poses botherations correlated with CNS-particular delivery in addition to longterm safety challenges. Further advancements would need improvementof i) targeted delivery techniques, ii) controlled gene expression, along with iii) confirmation in clinical trials to iv) totally appreciate the therapeutic plausibility of astrocytes in re- creating redox harmony subsequent to CNS damage. Although, substantial preclinical corroboration, plethora of barricades hindrances exist in the translational plausibility of astrocyte targeted antioxidative therapies. The BBB penetration continues to be a main pharmacological concerns,restricting the bioavailability of, i) several small-molecule as well as ii) gene- dependent compounds.

Additionally, sustained Nrf2 activation, i) despite protection conferring, ii) might result in inimical metabolic reprogramming or iii) disturb normal redox signalling iv) at the time of long-term delivery.

Furthermore, i) pharmacokinetic heterogeneity ii) across administration routes in addition to iii) disease circumstances iv) makes idealization of the dosage complex. Tackling such concerns would need a) novel administration systems capable of b) cell-particular targeting, c) transitory activation kinetics, along with d) incorporation with biomarkers which are capable of monitoring CNS redox states in vivo.

Although a little away from topic of NDD's and TBI-SCI etc but definitely part of OS-just wanted to highlight work of recent research where 3dimensional Healthcare (3DHC) was used for treating all disorders Insulin resistance(IR) generation with correlated diseases(Obesity, T2DM ,cancer Coronary Artery Disease(CAD) and Heart Failure with Preserved Ejection Fraction-total rectification of IR correlated diseases with how 3DHC-the significance in reference to this topic of OS being even in case of normal individuals with escalating Stressesof modern day life how it is of importance to follow the advice of supreme soul with getting rid of 5 vikaar or vices say normal EEG Activity in awake system should me α rhythm in basal stage & no waste thoughts,once existence of waste thoughts β rhythm starts in addition to with anger it escalatesgoing upto 30-35 as well as further anger unrest person stops realizing of what he is doing along with in tansient stage might commit even upto murder -the reason for all these being thoughts are energyconsuming as well as greater metabolic activity greater generation of free radicals as well as eventually all disorders generating with correlated escalated cortisol in 'Chronic Stresses we are living with resulting in plethora of diseases development all of which are reversible with 3DHC inclusive of rajyoga meditation without requirement of any medicine(exhaustively reviewedin 276).This is not just theoretical but based on how our brains get orders from soul located adjacent to hypothalamus,which we Scientists have not been able to catch till date although use of PET-MRI has labelled it gods point ,so in future use of such knowledge needs to be use to make Obesity, T2DM disappear within days to week with no need of medicine,with telomere length escalating subsequent to its use.This forced American Diabetes Association ADA to incorporate meditation in their therapy program of all CVD inclusive of CAD Despite not in agreement with the vested interests of pharmaceutical companies dictating the outcomes in this materialistic world.

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