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Review Article

How can we Avoid the propagation of Neurode generative diseases: Aiming on Concentrating and targeting the risk factors like aging, oxida tive stress, inflammation,glycation along with vascular injury –"A Systematic Review"

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Abstract

Neurodegenerative disease (NDD)is a common terminology utilized for variety of situations like Alzheimer's disease (AD), Parkinson's disease (PD), Huntingten's disease(HD), as well as, Amyotrophic lateral sclerosis(ALS), that to start with influence the neurons in the human brain. Extensive research has been concentrated on the modes as well as risk factors that are significant for etiopathogenesis that is a highly complex one of Neurodegenerative diseases. At present there is no available treatment that can cure NDD, with whatever therapeutic options that are available can just regulate the symptoms or postpone the propagation of the disease. Earlier we had tried to explore the influence of obesity, metabolic syndrome on how it is influencing the escalating incidence of NPD along with NDD. Further we concentrated on the role of utilization of momnoterpenes, iridoids in AD, engineering probiotics which might be efficacious in AD, PD. Hence here we conducted a systematic review for the various etiopathological factors for NDD utilizing the search engine pubmed, google scholsr, scopus, web of science, Cochrane data base from 1985-2020 till date. We used the MeSH terms like aging; alzheimers disease; parkin sons disease; Huntingten's disease(HD), Amyotrophic lateral sclerosis(ALS); oxidative stress; endothelial dysafunction; Advanced Glycation End Products(AGE's); Receptor for AGE(RAGE); MMP; NFκB; traumatic brain damage (TBI); Stroke; diabetes mellitus(DM); neuroinflammation; neuronal loss We found a total of 451, 956 articles out of which we selected 186 articles for this review. No meta analysis was done. Thus, in this review, we have detailed the complicated network of molecular modes underlying acute as well as chronic Neurodegeneration, concentrating on the impairment in redox homeostasis, underlying a shared mode for the 5 risk factors namely aging, oxidative stress, neuroinflammation, glycation as well as vascular damage. Thus, any avoiding strategy that targets mutip; e factors together at an early styage are the ones having maximum chance of arresting propagation of Neurodegenerative disease (besides lot of plant product, curcumin, resveratrol, iridoids and attacking epigenetic alterations.

Keywords: Neurodegenerative diseases; alzheimers disease; aging; parkin sons' disease; Advanced Glycation End Products; DM; resveratrol; iridoids; curcumin

Introduction

Neurodegenerative disease(NDD) by definition isachronic problem having different sequential implicationsassociated with motor, sensory aswell as perceptual impairmentsthat result in both cognitiveaswell as behavioural deficiencies. Selective neuronalcellloss presents in adulthood,in various regions of the brain [1]. There are 2 kinds of NDD, namely acute aswell aschronic [2]. Alzheimer's disease (AD), Parkinson's disease(PD), Huntingten's disease(HD), Amyotrophic lateral sclerosis(ALS) etc. which share multiple features like oxidative stress,glycation,aberrant proteindeposition, inflammation, aswell ascontinuing neuronalcellloss [3]. Earlier we have reviewed on how associated with obesity and metabolic syndrome incidence of NPD and NDD is increasing and how in cases of DM (T1D or T2D) can be associated with escalated atherosclerosis with association of Advanced Glycation End Products (AGE's) and Receptor for AGE (RAGE) and how small molecules from plants like monoterpenes, iridoids might be utilized in treating AD along with engineering newer probiotics be used to treat AD aswell as PD [4-7]. Significantly it gets emphasized that lot of years of traumatic brain damage (TBI) or stroke patientshave demonstrated an enhancedincidenceof Neurodegenerative diseases that become chronic [8,9]. Specifically, followinga TBI, many patientsdemonstrate motor aswell as cognitive presentationsakin to the ones seen in (AD aswell as PDpatients [10]. In the last century escalatedfocus has beendevoted to

the isolation of modesaswell as risk factors resulting in the complexetiopathogenesis of NDD, that arebesides genetic, vascular, aswell as metabolic, lifestyle – associated factors thatusually coexistaswell as crosstalk with each other [11,12].

Due to complicatedmultifactors involvedin etiopathogenesis of NDD,strategies which target a lot of risk factors at same timeaswell as disease modesat an early phase of the disease have the maximum chancesto become efficacious. Of themultiple factors that could explain the probable etiopathogenesis of NDD, aging represents a primary risk along with cerebrovascular disease (CVD), diabetes mellitus (DM) aswell as inflammation,show stepsin inevitablecomplex cascade [13]. The actionsof the variety of risk factors are based on age of patient, at the initiation oftreatment, pointing thatthe timing of avoiding targetingrequires careful attention.

Inflammation, represents, a crucial correlatorassociating vascular impairments as well as Neurodegeneration. Actually inflammation, Specifically, of endothelium, remains centralfor the startingalong withpropagation of a wide spectrum of age –correlated Neurodegenerative diseases [14], aswell as it has been shown to influence the expression of brain derived neutrotrophic factor (BDNF) within brain [15]. Neuro inflammation represents a crucial factorin case of both acute aswell as chronic problems[16,17]. Ascomparedtoother tissues, in the case of central nervous system(CNS),-cellular invasion secondary toinflammation, infection, or damageis weaker along with delayed. Nevertheless, microglia, central aswell as the expressionalong withthe liberation of classical inflammatorymediators,like acute –phase proteins, eicosanoids, complements as well as cytokines get stimulated fast[18-20].

Furthermore, redox signalling impairmenthas been observed to be an aiding factorin various age-associated diseases, along with causes ,endothelialimpairment inmost of these pathophysiological situations [21].That radical detoxification pathwaysbecome crucialhomeostatic modesin correlation with vasoprotection in case of agingaswell aschronicde generative diseases [22], has been revealedby a lot of studies. Additionally, oxidative stress I s further associated with the dysfunction of the blood glucose control[23].

Nuclear factor(erythroid –deri ved 2)-like 2 (Nrf2) as well as Nuclear factor-κ B(NF-κB)represent 2 intercommunicated mastercontrollers of cellularresponses to oxidative stress as well as inflammation,respectively24]. Alot of studies demonstrated recently that signalling impairment inredox homeostasisare the usual modesincardio vascularsystem(CVS), neurologicalaswell as metabolicdiseases [25]. Nevertheless, oxidative stress could not target pharmacologically as well as the only approach experimented so far, utilizing antioxidants was not successful or might turn out to be deleterious as well. Significantly, small moleculeshave now become available have the capacity to crossreactwith particular, targets as well as are helpful for therapeutic evidenceor proof – of –concept-studies. The significance of evaluating this complicated cross-associated molecular modesbehind NDD onset aswell as degeneration seememphatic. For detailing thepropertiesof these complicated networks of modes which are behind acute aswell aschronic neurodegeneration, the aim of this reviewis to concentrate on the redoxhomeostasis,as the usual modesbehind the 5key risk factors namely aging , oxidative stressinflammation, vascularinjury, aswell as glycation.

Significance of oxidative stress as well as aging in Chronic Neurodegenerative disease

The commonest cause of dementia worldwide is AD,leading to 60-70% of patients (http://www.who.int/media centre/factsheets/fs362.en/), although enhancing incide ncedepicts that mixed brain etiopathologies (AD aswell asvascular) representing maximum dementiapatients in old age [26]. Earlier therapy work concentrated on management of single risk factors with not much success.

Without any doubt aging remains the initial risk factor for Neurodegenerative disease, as well as age –correlated alterations in cellular function makes a person prone to the etiopathogenesis of varying conditions like AD. The EU population that is ≥65 is anticipated to doubleby 2030 aswell astriple by 2050 [27]. Besides making a person more prone to NDD, aging further interferes with the self repair capacities. At present the total number of caseswho are living with NDD, worldwide is at present thought to be about 50million (http://www.who.int/media centre/factsheets/fs362.en/). The economic - social burden of NDD besides having a drastic impact on patients along with their families aswell as caregivers. Actually the massive cost of the diseases would be a huge burdenon the health systemto tackle the anticipated future escalatation of prevalence. With the molecular advancement evolution, insightof aging as well as cognitive deterioration continuously is escalating. Alot of signalling pathways implicated in the control of aging as well aslifespan have been found, as well as recent studieshave shown that these signalling pathways are implicated in agingcorrelation with cognitive deterioration [28]. These pathway might be the significant targetsfor forming innovative aswell as efficacious disease manipulating drugs for therapy, Delaying or avoiding aging correlation with Neurodegenerative disease.

To our misfortune till date, no efficacious treatment are at our disposalfor stopping or slowing the death as well as mal function of neurons in the brain, responsible for disease symptoms as well as result in fatality of disease. Hence forming newer approaches as well as drugs for slowing downthe initiation as well as propagation of neurodegenerative disease is the basic aim, which might result in significant influence both from the socialalong with economic influence. β-Amyloid (Aβ)plaquegetting deposited aswell as neurofibrillary tangle (NFT) collection besides being labelled as neuropathological landmarksof AD, have further been widely ascribed as well as detailed in the healthy aging event [29]. The chronic enhancement of oxidative stress has been appreciatedin the form of a crucial factor aiding in aging as well as various age – correlation of diseases. Actually ''theoxidative stresstheory of aging", takes into account the functional dysfunction correlated with aging, secondary to the collection of oxidative damage to lipids, DNA as well as proteins by reactive oxygen species (ROS), as well as reactive nitrogen species (RNS). Never the less, the precise mode by which oxidative stress stimulates aging is still not clear. Probably the enhanced amounts of ROS as well as, RNS result in cellular senescence, that implicates the liberation of soluble proinflammatory factors aswell asdegrading enzymes [30]. S-nitrolysation, a covalentreaction of a nitric oxide (NO) group with a reactive cysteinethiol group on target proteins, has evolved as the main mode influencing NO bioactivity [31]. S-nitrolysation, control proteins function as well as can modulate either protection or neurotoxic actions based on the action of the target proteins [32]. In normal physiological situations, NO generation stimulated by GMPc activation forms mitochondrial biogenesis via peroxisome proliferative activated receptor gamma (PPARy) coactivator. as comparedto that enhanced nitrosative stress can cause deficiencies in mitochondrial function. Like S-nitrolysation influences mitochondrial respiration via inhibition of complexes I-IV [33]. Significantly Cho et al. showed that S-nitrolysation of Drp 1 modulate Aβ stimulated interference with mitochondrial dynamics, leading to synaptic injury as well as neuronal damage [34]. Hence protein alterations generated by RNS might interfere with mitochondrial health as well as further stimulate synaptic impairment as well as neuronal death. Actually, another factor visualized in AD brainsis mitochondrial impairment [35], having the properties of enhanced mitochondrial membrane permeability as well ascorrelated with the liberation of cytochrome c [36]. Significantly, Antequera et al.[37] observed a decreasein the expression amounts of mitochondrial complex 1 as well as III. They posited that this is mitochondrial impairment is possibly secondaryto Aβ- correlated mitochondrial impairment gets aggravatedby aging.The posit is that the enhanced amounts ofAβ- as well as the aging eventin AD patientscould be attributed the senescent phenotype that further implicates endothelial cells impairment as well as having the properties of enhancedoxidative

stress [30]. Zhu et al. in a recent publication demonstrated in aging mouse model (SAMP8), the cognitivedys function, inflammation as well as oxidative stress that got very efficaciously corrected by treatment with ligustilide, the major biological active component thatexists in Angelica sinensis, a perennialplant, belonging to the Umbelliferae family [38]. Lot of studies have demonstrated the capacity of ligustilide to be able to get across the blood brain barrier (BBB) as well as to arrive at the CNS where the active component canevoke itsanti oxidative as well as antiapoptotic actions [39]. The basic part of oxidative stress in Neurodegenerative diseases has been appreciated , as well as in initial stages, it is feasibleto see a significant, enhancement of ROS generation [40].On effectively taking care of this process, the cognitivedys function, as well as the inflammatory event get successfully tackled [41]. A close correlation exists among oxidative stress, aging as well as inflammation.

At the time of aging, the chronicoxidative stress escalates the absence of homeostasis, improving Specifically, the controlling systems, like the immune response. This situation stimulates the inflammation, which in turnescalates oxidative stress and thus forming a vicious cycle [42]. Escalated bio markers for oxidative stress are associated with high amount of inflammatory cytokines, as per a recent study, with both being responsible for the poor cognitive abilityof aged patients [43]. A lot of studies have demonstrated that cognitive fall is slower when endogenous oxidant systems, like glutathione peroxidise (GSH-Px), are high. Conversely high amount of GSH escalate cognitive dysfunction, in case of aged patients [40, 44]. This is a controversial process, since GSH is believed to confer endogenous protection against intracellular oxidative stress . The reasoning for this might be, since GSH is a substrate for GSH-Px, the enhancement of GSH amount might be secondary to the enhancement of oxidative stress associated with the fall of GSH-Pxaction [45]. This escalated amount of oxidative stress was observed human peripheral blood mononuclear(PBMN) cells removed from patients presenting with mild cognitivedyfunction as well as from 3 mths old 3x Tg-AD male mice, that was possibly secondary to the escalated amount of Nrf 2 as well as decreased superoxide dismutase1 (SOD1) mRNA in the brain cortex [46]. That Nrf2 is believed to be the main controller of the cellular response to oxidative as well as toxic insults, manipulating the expression of upto hundreds of genes that influence immune as well as inflammatory response, cellular metabolism as well as metabolic control, as well as cognitivedys function along with addictive behaviour [47]. The control of Nrf2 is complicated as well as regulated besides by the repressor protein Kelch ECH associating protein 1(Keap1) but further by other signalling pathways, that are GSK-3, NFκB, NOTCH as well as AMP kinase [44, 48]. In the view of part of Nrf2 impairment in Neurodegenerative diseases. At present Nrf2 inducers are getting evaluated. The AT- Nrf 2- Knockout mouse model, that combines amyloidopathy as well as tauropathy with Nrf2 deficiency, presents enhanced markers of oxidative stress as well asneuro inflammation, in the brain tissue as compared to wild type mioce [49]. Moreover, young adult AT- Nrf2-Knockout mice have demonstrated deficiencies in spatial learning as well as decreased longterm potentiation. Transcriptomic evaluationhas demonstrated that Nrf2-Knockout mouse brains share 7 as well as 10 of the maximum dysregulated pathways with aging human as well as AD brains respectively [49].

Aging as well as Neuroinflammation-Part of Acute Damage as well as Influence on Neutrophins

Of the mainetiologies of a Acute Brain damage, TBI as well as stroke are the most significant. Both primary as well as secondary, injury modesre present the etiological modes of TBI, a highly complicated condition [50]. i) Primaryinjury modesoccurdueto mechanicaldamage of neurons, axons, glia, as well as blood vessels secondary to shearing, tearing, or by stretching. 2) secondary injury modes are different kinds of events like depolarizations along with ionic homeostasis alterations [51], ii) liberation of neurotransmitters (like glutamate excitotoxicity)[52], mitochondria impairment [53], iii) apoptosis of the neurons [54], iv) lipid breakdown [55], inflammatory as well as immune response starting [56].

Similarly strokes might be divided into 2 major kinds i)ischaemic iihaemorrhagic.The neurological impairment occurs secondary tofocal cerebral, spinal, or retinal infarction in the 1st kind. For the, haemorrhagic strokethe division is i) subarachnoid haemorrhage (SAH), II) Haemorrhage from acerebral bloodvessels, aneurysm, or vascular maldevelopment in the subarachnoid space, or in the form of intra cerebral haemorrhage (ICH) where a blood vessel that has become a little weak within the brain gives way, that result in leakage as well as enhanced intracranial pressure, resulting in injury to the brain cells that surround the blood [57]. Neuroinflammation, which occurs following trauma, has the properties of oxidative stress, glial cell getting activated, recruitment of the leukocytes, as well as liberation of inflammatory mediators [56], like detailed after this. High ROS amount results in lipoperoxidation of the cell membrane, resulting in mitochondrial impairment as well as oxidizing of proteins [58]. Following injury, endogenous inflammatory responses getactivatedfor protection of thearea that gets injuredvia pathogens invading as well as for restoration of damaged cells. In such situations, their is activation of the complement system, that is followed by infiltration of lymphocytes, monocytes, as well as, neutrophils via the blood brain barrier (BBB) [59], that ultimately causes generation of prostaglandins, pro inflammatory cytokines. Microglia represent the innate immune cells within the CNS along with being the initial cells as the 1st line of defenceafter brain damage [60]. Conversely, on over activation, they might stimulate harmful neurotoxicalteration via liberation of a lot of cytotoxic agents, like pro inflammatorycytokines as well as oxidativemetabolites [61]. Moreover, the liberation of pro inflammatory cytokines as well as rest of the soluble factorsby microglial activation can implicate the following activation of the astrocytes[62].

Once activated, the seastrocytesupregulate various Neutrophic factors (like BDNF) which protectsfrom cell damages [63]. Additionally, astrocytes have a key part in controlling excitotoxicityby decreasing glutamate amounts at neuronal level [64]. These changes might result in any secondary kind of neurological disease, like ischaemia as well as epilepsy [65]. Following injury, neutrophils represent the initialimmune cells which go through conformational alteration as well as migraine via the endothelial vessels wall as well as invasion of the injured tissue [66]. Subsequent to an ischaemic injury, neutrophils result insecondary damageby liberation of pro inflammatory factors, ROS, proteases as well as matrix metalloproteinases (MMP'S) [67]. Such toxic factors interfere with EC membrane as well as basal lamina resulting in enhanced BBB permeability [19]. Additionally, leukocytes escalate ischaemic damage that blocks theerythrocytes' flow aswell as then stimulation of proteases, reactive oxygen species (ROS) as well as MMP'S, which can markedly cause injury to bloodvessel as well as brain tissues. Lastly, the leukocytes, that infiltrated further escalate neuronal damage by stimulation of pro inflammatory factors in as well as around the penumbra or potentially salvageable brain tissue around the primary tissue damaged, as well as the infarct core [19, 68]. Expression of cell adhesion molecules(CAM) gets upregulated via cytokines [69], since the intra cellular adhesion molecules (ICAM 1) in the ischaemic core causes BBB getting disrupted [19]. The 3 main pro inflammatory cytokinesare tumor necrosis factor alpha (TNF-α),interleukin 1 beta(IL-1β), as well as IL-6 which aid in the inflammatory response, following brain injury [70]. Following some stimuli TNF-α gets generated as well as liberated by microglia, astrocytes along with. or byneurons as well as gets implicated in escalating the BBB permeability, besides manipulating the synaptic transmission as well as plasticity [71]. Following the generation of an inflassome , IL-1β, can result in NFκB getting activated through toll like receptors (TLR's) that aids in the nuclear factor to transactivate genescorrelated with cytokines, chemokines as well as rest of pro inflammatory mediators. Additionally, IL-1β, has the ability of priming the endothelium for escalation of leukocytes sticking as well as edema generation [72]. Further Yang et al., showed that IL-6 works in the form of an acceleration signal with regards to the inflammatory response along with motor coordination

following brain damage[73].

The age at the time of injury has a big chance of implicating the method by which brain can heal it self along with the status of development, degree of cellular senescence, as well as injury – stimulated inflammation, [74, 75].Hoane et al., as well as Sohrabji demonstrated that aging enhanced the basic risk factor for the ischaemic stroke [76, 77]. This is possibly secondaryto the functional alterations which presented in the BBB secondary to brain injury, implicating reduced trafficking of peripheral immune cellsinto the parenchyma of the brain as well as enhanced oxidative stress as well as inflammatory mediators liberation which results in an amplification of the inflammatory response in the damaged brain [78]. Due to this the insight of cell particular alterations in the brain that is aging would prove to be key to form the next generation drug treatment.

Since the molecular modes of aging in mice is akinto the ones in humans [71], mouse models have got commonly utilizedin the field of neurodegenerative diseases-related with aging [79]. Specifically, studies carried out to concentrate on main risk factorsfor PD, documented to be correlated with aging [80]. Crupi et al. had already documented regarding PD modeled on old mice by 1-methy l-4-phenyl-1,2,3.6-tetrahydropyridine (MPTP). Specifically, old MPTP-intoxicated mice (21 mths old) awa as well as young MPTP-intoxicated mice (3mths old) were given the behavioral evaluation as well as brain processing 8 days following MPTP delivery [81]. Crupi et al. [81], showeda > significant nigrostriatal dopamine (DA) degenerationas comparedto that seen in young MPTP-intoxicated mice. Further more, anxiety like behaviors was more obviousin old MPTP-intoxicated mice. Here the objective of Crupi et al., was to mark a window for utilizing treatment to negate the Neurodegenerative event efficiently that are correlated with age –linked diseases. Actually present treatments do not tackle neuro inflammation, Nevertheless, though neuro inflammation, might aggravatePD diseaseevent, they are just concentrating onabrogating the symptoms of DA deletioninstead of the mode behind the DA neuron injury [82].

A NDD-correlatied with inflammation as well as oxidative stress, might form secondary to brain injury, evaluating the initiation of neuro degeneration in MPTP mouse models, in young as well as aged animals can be believed to be a an attractive basis. Calabrese et al, regarding this revealed that peripheral as well as/or central inflammatory stimuli, influencing the brain, might stimulate inflammatory alterations resulting in PD symptoms as well as propagation [83].

The aberrant neuro inflammatory event as well as oxidative stress might have a bad influence on neuroplasticity, the capacity of brainto receive as well as respondto any external as well as internal stimulus via an adaptive mode, that gets compromised in lot of NDD [83]. The CNS ability to shape both structure as well as function, to manageis based on an integrated implication of various molecular systems, of which Neutrophic factors (NF's) have a key part. Actually, one is quite aware that the density as well as specialization of the resident CNS cellular populations are secondary to a lot of complicated events. Proliferation, differentiation, growth, migration, synaptic generation as well as manipulation are basically all done by NF's, especially neurotrophins(NT).

NT's represent a group of polypeptide growth factors liberated by various brain cell populations like microglialcells. oligodendrocytes, astrocytes as well as neurons. The NT family comprises of separate but polypeptides that are akin to each other; nerve growth factor (NGF), BDNF, NT-3, NT-4/5, along with the recent addition of NT-6 as well as NT-7. Their action gets modulated by binding to particular transmembrane receptors, like the troponin receptor tyrosine kinase (Trk receptors) as well as the p75 NTreceptor. Separate binding affinitiesare possessed by various NT's like NGF binds to TrkA, BDNF as well as NT-4 to TrkB as well as NT-3 to TrkC, while all 4 can bind to the p75 NT receptor. Moreover, the correlation of p75 with Trk receptors can enhance the particular affinity of the 2nd ones for every respective NT' [84]. These days the part of NT for the,g enerating neuronshas been well established [85]. Never the less, the concentration of the research has shiftedon their, function as mediatorsof neural as well as synaptic plasticity in the adult brain. Specifically, BDNF has come out for its part in a lot of neurophysiological event. Specifically,curious activity based control, as well as in view of too much amounts, implications in neuroplasticity, right through out the full life span. A lot of action where BDNF is implicated, depends on its genetic structure whose properties have been worked out in detail [86]. The BDNF gene comprises of lot of promoters which drive the expression of various transcripts having separate non-coding exons. Significantly, separate isoforms of BDNF get expressed in various subcellular compartments, like exon IV mRNAs have found in the soma as well as dendrites, where as exon III expression is limited to the cellbody [87]. What is Significant to observeis that the transcripts which target dendritic region might facilitaterapid local translation of both pro as well as mature BDNF, generating an action that is strictlycorrelated with the synaptic structure as well as action [88]. The generationof the mature BDNF is thus a complicated event, implicating separate precursor isoforms as well as separate probable path ways for achieving the mature form. The pro- BDNF protein, actually can get cleaved both with in theintra cellular space, in the intracellular liberating vesicles, or following, liberation, via separate mode. Pro BDNF also acts as an active precursor that can bind the p75 neurotrophins receptor as well as sortilin receptor, where as mature BDNF bind the p75 receptor as well as with preference TrkB [89]. On binding with , TrkB stimulates dimerization as well as auto phosphorylation.On phosphorylation. TrkB stimulates a sequence ofintracellular path ways like phosphatidyl inositide -3 kinase (PI3K) /protein kinase B (PI3K/Akt) correlated pathways, that possess anti apoptotic as well as prosurvival actionsawa mediate N-methyl –D-aspartate receptor(NMDAR), based synapticplasticity [90, 91]; the PI3K/Akt/mTOR (mammalian target of rapamycin) cascade which via control of protein generation as well as cytoskeleton generation, escalates dendritic growth as well as branching [92], Mitogen associated protein kinase (MAPK)/ Ras signalling cascade which controls protein generation, during neuronal differentiation [93] as well as many rest .

Knowing the key physiological part that BDNF influences via the abovedetailed modes on various events that we knows get compromised in NDD, like survival as well as cognition, various clinical as well as pre clinical studies evaluated the effect of risk factors for these diseases on BDNF function, in Specifically, concentrating on the part of aging. The out comes derivedtypically demonstrated besidesan association among aging as well as deficit in neuro plasticity but further among BDNF changes as well as frailty, the fragility that mightbe a part of NDD in the elderly [94]. Additionally, it is significant to see that certain persons can reach advanced age with most of the cognitive functions being normal while rest for ma situation of frailty, with the properties of enhanced generally being pronesecondary to micro traumas as well as a harmful processes that have collected throughout life. Moreover, even the elder individuals who had been at high function level as well as go through an acute injury like TBI or stroke), a stress or infection become at great erriska situation of forming a temporary or permanent cognitive dysfunction, that might in turn cause dementia as well as other symptoms of NDD. Till now, the cognitive dysfunction seen in elderlyis secondary, at least partlyto structural as well as physiological alteration in the brain. At the time of aging, these eventsgo through a physiological deterioration as well as structural alteration in the neuro transmitter receptor expression as well as alterations in electro physiological characteristics take place resulting inenhanced proneness towards neurological diseases[95].

For trying to reason out the alterations seen at aging time, a negative association among BDNF serum amounts as well as aging has been observed in healthy individuals [96]. Further more the hippocampal volumeof 142healthy individuals among 59-81yrs agehad been evaluated as well as

associated with BDNF serum amounts as well as memory performances, observing that enhanced age was correlated with smaller hippocampal volume, decreased BDNF serum amounts, as well as poorer memory performances [97]. Further a post-mortem studyon healthy individuals among 16 to 96yrs corroborated this negative association among BDNF serum as well as age in or bitofrontal cortex (OFC), as well as demonstrated that the expression of synapse-associated genes that were from the BDNF network got down regulated with age also [98]. Of the modes which might influencethe BDNF systemat the time of aging, an aberrant activation of the immune / inflammatory system is believed to be a significant candidate. Actually, it is well understood that inflammatory response might inflence neuro plasticityat the time of formation as well as adult hood [99]. Further more at the time of aging, the immune systemgoes through dysfunctionwhich resultsin a chronic systemic inflammation, with enhanced amounts of cytokines, chemokines, pro inflammatory enzymes as well as transcription [100].

The ''inflammaging"state does notrule that brain, in the form of peripheralcirculating small molecules like cytokines, have the ability of infiltrating the central nervous system (CNS) via the BBB, that stimulatesa cerebral stated of neuro inflammation which can get amplified more by the microglial stimulation [101]. Regards to this it has been documented that the macrophages activation gets particularly modulated at the time of aging, pointing to a probable part of oxidative stress [102]. In physiological situations, microglial cells seem to bein a resting state where they actively survey the CNS surroundings, immediately prepared to act in case of a harmful stimulus takes, place, with morphological alterations as well as generation of cytokines as well as of proliferative as well as macrophagic factors [103], after –the threat either in form of infection or damage has got deleted towards another state, with the properties of a gene profile that can facilitatetissue healing as well as reconstruction via the generationof anti inflammatory cytokines, growth factors as well as neurotrophins like BDNF [104]. At the time of aging, microglial cells go via a series of modulations like telomere shortening as well as cellulardystrophy causing its death. Streit et al., watched in a post-mortem experimental, study, significantly greater degenerational alterationsin microglia ofelderly (>68yrs) as compared to, younger individuals (38yrs) [105]. Significantly it has been documented that degenerated or senescent microglia might go through age based dystrophy, resulting in neuro protective functions might get, hence escalatingthe risk of forming NDD [106]. Ritzel et al., utilizing flows cytometryin mice isolatedan important population of side scatter –high microglia with in the brain of the elderly which showed functional aberrations as compared to younger microglia that are greater generation of ROS as well as pro inflammatory cytokines, enhanced mitochondrial amount as well as low phagocytic capacity [107]. Moreover, microglia cells ofelderlyform a pro inflammatory state secondary, to reducedresting signalling of neurons as well as astrocytes [108]. Due to this outside stimuli (like stress, injury as well as infection) can switch the eldely brain with ease into a state of mild chronic neuro inflammation, that makes the brain having greater vulnerability towards apoptotic signalling [109], resulting in absence of volume as well as cognitive dysfunction [110, reviewed in ref 111](figure1).

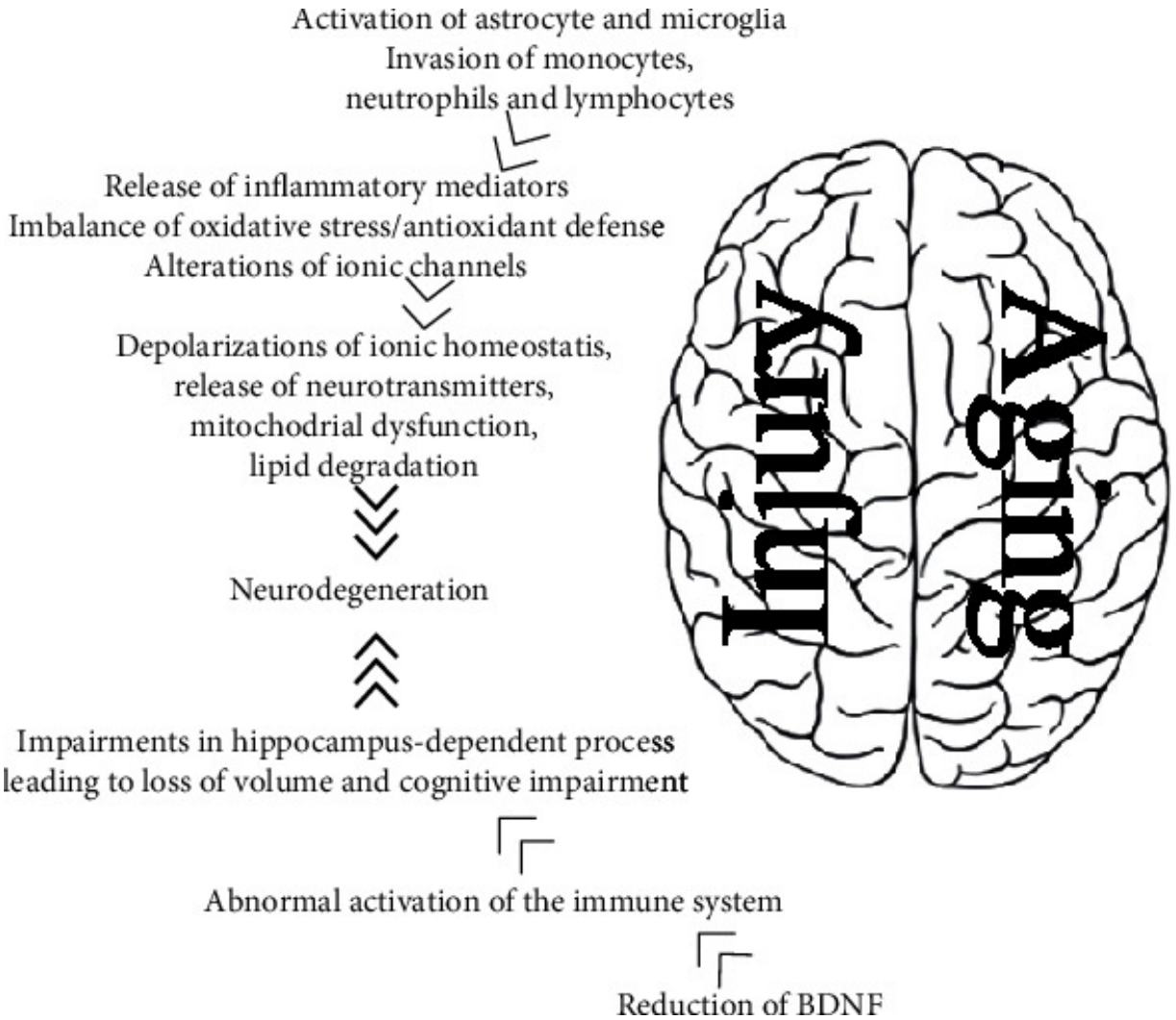

Figure 1: Courtesy ref no-111- Contribution of inflammation, oxidative damage, and reduction in NT levels to neurodegeneration in aged brain after injury.

Specifically, preclinical studies showed that enhanced hippocampal amounts of IL-1β, interfere with the carrying out of behavioural paradigms mostly utilized for evaluation of hippocampal-basedcontextual tasks after intraperitoneal (ip) [112], or intra hippocampal IL-1β injection[113] as well as, enhancement of endogenousIL-1β, induced via infections [112, 113] or psychological as well as physical stressors [114].

This aging based low grade chronic inflammation, is believed to aid in the decrease of BDNF amount seen in elderly population. A preclinical studyconducted via Guan as well as Fang, showed that a peripheral injection of lipopolysaccharide (LPS), that is a robustcytokine stimulator, results in a decrease in protein amount of BDNF in various cortical areas along with hippo campus of adult rats [115]. In mice as well these results got corroborated, in which decreased amount of protein of pro BDNF, mature BDNF, as well as BDNF m RNA amounts have got observed in synaptosomes 3 days following the LPS ipinjection [116]. Akin to these out comes were seen in old animals 5days following the inflammatory challenge. particularly, aged rats got exposed toE. Coli Ip-intraperitoneal by Cortese et al [117], for stimulating a peripheralinflammatory response, observed decreased amounts of mature BDNF as well as TrkB activation as comparedtold rats who got exposed toE.Coli [117]. Moreover the central deliveryof a receptor antagonist ofIL-1 along with E.Coliinjection could block the decrease of BDNF amount that was seen [118], along with correlated long term memory dysfunction initiated by E.Coliinjection [119]. Agreeing with these findings, the infusions of pro inflammatory cytokine IL-1β in the hippocampus, reduced the stimulation of BDNF gene expression stimulated via contextual fear conditioning [118].

Mode of Neurodegeneration Correlated with endothelial cells Impairment

There is an overlap of lot of vascular risk factors, like age diabetes mellitus (DM), hypertension as well as hyper cholesteremia with those of ND risk factors in older patients, along with vascular Impairment being known to determine NDD like AD, cerebral amyloid angiopaty (CAA), PD, as well as ALS [120]. The integrity of the BBB, in the form of a neuro vascular unit (NVU), is necessary for sustaining enough perfusion of the brain along with the brain functioning as well as for preserving normal neurologicalfunctions. oxidative stress has a key part further on pathological BBB dysfunction as well as on cerebro vascular Impairment seen in NDD.

AD, has the properties of enhanced Aβ protein which results in the destabilization of vascular intactness that ultimately facilitates leakage from vessels. Absence of vascular intactness presents as EC detaching from the BM, double barreling of the vessel walls , as well as aneurysm generation. These processesusually end in blood getting extravasted towards the perivascular space as well as in the starting of theinflammatory response, that has the properties of NDD. Various studies have definitely demonstrated that the pathological amount, the range of micromolar, of various Aβ peptides, Specifically, the shorter vaculotropic $A\beta_{1\text{-}40}$ variant as well as the Aβ mutants, have a correlation with specific hereditary phenotypesof CAA as well as alter angiogenesis as well as vascular sustainance by escalation of cellular oxidative stress. The vascular injury stimulated by Aβ are changes in the vascular tone, dysfunction of the vascular remodeling as well as deletion of barrier functions, along with repression of the intrinsic angiogenic characteristics of the endothelium.

$A\beta_{1\text{-}40}$ peptide as well as its Dutch variant was shown by Donnini et al., to result in premature senescent phenotypes in EC's in both zebrafish embryos as well as human EC's [121]. Further $A\beta_{1\text{-}40}$ peptide has been documented to result inmitochondrial dysfunction as well as reduces the aldehyde dehrogenase (ALDH2) detoxifying enzyme action in EC's in, causing cellmembrane dismantling as well as deficiency in permeability [122]. Akin to thatthe $A\beta_{1\text{-}40}$ peptide, has been documented to stimulate endoplasmic reticulum stress (ER) stress in ratsbrain EC's, ultimately causing vascul ardefects [123]. The molecular modes of theselots of $A\beta_{1\text{-}40}$ stimulated actionson EC's, are complicated as well as might be direct as well as in direct cross talk with angiogenic growth factors, like vacular endothelial growth factors (VEGF) as well as fibroblast growth factors (FGF2).

FGF2 signalling is a significant path way implicated in the sustainance of intactness of quiet vasculature. That $A\beta_{1\text{-}40}$ as well as its arctic E22G as well as Dutch variant E22G variant cause down regulation of FGF2 generation as well as FGF2 stimulated Akt activation was demonstrated by Solito et al. Further more $A\beta_{1\text{-}40}$ as well as its variantinhibit FGF2 binding to heparin along with FGF receptor1 phosphorylation, in vivo as well as in vitro [124]. Significantly, vascular intactness disturbance caused by $A\beta_{1\text{-}40}$ of FGF2 signalling can get rescued that results in over expression of FGF2 in EC's. Actually, EC's over expressing FGF2 demonstrated significant resistance towards $A\beta_{1\text{-}40}$ stimulated damages. This FGF2 mode implicated in prevention of damage implicates the downstream escalatation of Akt as well as the endothelial NOS (eNOS) stimulation [125].

Various studies demonstrated that Aβ further influenced vascular endothelial growth factors (VEGF) signalling. In AD mouse modelsthe VEGFreceptor -2mRNA as well as the protein amount get significantly reduced following $A\beta_{1\text{-}40}$, in EC's as well as brain [125]. That $A\beta_{1\text{-}42}$ inhibits VEGF stimulated migration of EC's was demonstrated by Patel et al., [126], that competes with its receptor VEGFR [126]. Further more, cell culture studiess howed that at pathological amounts Aβ works as a VEGF antagonist, that inhibitsthe VEGF stimulated tyrosine phosphorylation of VEGFR2, along with VEGF stimulation of Akt as well as endothelialnitric oxide synthase (eNOS) phosphorylation in EC's [126, 127].

Expression of Aβ precursor protein (APP) occurs in various cells as well as tissues like brain, kidney, platelets as well as vascular endothelium of cerebral as well as peripheral bloodvessels. significantly, various studiesdemonstrated a vascular function of APP as well as/or Aβ on EC's[128]. In case of cultured cerebral as well as peripheral EC's, nanomolar (nm), amounts akin to the physiological amounts of either $A\beta_{1\text{-}40}$ or $A\beta_{1\text{-}42}$ peptides facilitated angiogenesis by escalatation of growth migration as well as branching of tubes [129]. Hence oxidative stress gets stimulated by EC's in case of high amounts of Aβ peptides, that collect in the vessels of BBB as well as brain parenchyma. Never the less, physiological amounts of Aβ peptides are also needed for the homeostasis of the endothelium as well as escalatation of proof emphasizesin various organs the significance of APP as well as its metabolitesin aiding the function of the vascular tissue [127, 130]. The proof that clinical trials with the objective of targeting Aβ with immunotherapy have not worked as well as, in certain cases have been deleterious, recollects the physiological part of Aβ as well as its precursor protein APP in the vasculature. More workis requiredto find out why EC's express high amounts of APP as well as Aβ along with the functional part of these molecule at the vascular level.

Oxidative stress as well as mitochondrialImpairment represents critical factors during NDD is well understood. The mitochondrial enzyme ALDH2 has been demonstrated to possess a key partduring the neurotoxicmodes of these pathologies [131, 132]. The mitochondrial derangement might facilitatethe generation of reactive oxygen species(ROS), that enhancedthe pronenessof the cell towards oxidative stress. One of the sequelae of enhanced oxidative stress is the over generation of toxic aldehydesby lipid peroxidation from the mitochondrial membranes. Reactive aldehydes collection might inhibit ALDH2 as well as trigger mitochondrialImpairment resulting in greater aldehyde stimulated injury in both vascular as well as neural tissues. The superfamily of ALDH has a key rolein a lot of biological eventsthat are generation as well as detoxificationpathways with in the organism [133]. Specifically, mitochondrial ALDH2 is key in the oxidative metabolism of toxic aldehydes within the brain, like catecholaminergic metabolites (DOPAL as well as DOPEGAL) along with 4-hydroxy -2 nonenal-(4-HNE), which represent the main product of the lipid peroxidation event [178]. Inhibition of ALDH2 activity significantly

inhibit EC function have gotshown by recent studies, facilitating senescence [134, 135]. Absence of ALDH2 action decreases cell proliferation as well as migration along with cell permeability in EC's. Despite the mode of action has not got worked out, these studies pointthat the collection of these reactive aldehydes like 4-HNE as well as generation of ROS represent the major reasons of endothelial Impairment [134].

Escalation of oxidative stress, partly secondary to generation of Aβ plaque as well as NFT's in cases of AD as well as PD, can be also secondary to an absence of detoxification action of ALDH2. This posit getsverified by the association among ALDH2 loss of function mutations as well as a greater incidence of AD[133]. Furthermore, ALDH2-knock outmouse modelsdemonstrate both neuronal as well as vascular pathological alteration correlated with AD [135]. Aβ peptidetoxicity in returncan further inhibit mitochondrial ALDH2 action [122]. Significantly, this study demonstrated that the activation of ALDH2 possesses a protective part in endotheliumagainst insult by $A\beta_{1\text{-}40}$ [122]. Treatment, with ALDH2- particular- stimulation, Alda-1, has a significant protective role in mitochondrial function as well as decreases neuronal cell death within animal models of parkinsonism [132, 133, 136]. Secondary, to the key part in the sustainance of mitochondrial normal function, the utilization of activators of ALDH2 would confer protection against both neurons as well as vessel from neuro toxicity, hence activators of ALDH2 might be significant treatment target for the therapy of NDD.

Neurotoxicity secondary to Advanced Glycation end Products as well as their impact on Redox Metabolism

Neurotoxicity modulated via neurodegeneration can get stimulated by glycation reactions. The early Glycation adductsmajorly comprise of Amadori products formed via the reassembly of Schiffbases, constitutes a reversible event, early glycation adducts can further reorganize via cyclization, oxidation, dehydration or concentration reactions resulting in irreversibly bound adducts called Advanced Glycation End Products (AGE's) [138, 139], mostlycausing protein cross links [140]. As Glycation represents a nonenzymatic event, proteins having the properties of slow turn over are the ones that collect with ease as (AGE's) [138]. AGE generation was first evaluated in human tissues regards to escalated blood sugaramounts as well as diabetes, Never the less, more recently, other compounds like glyceraldehydes, glycoaldehydes, glyoxal as well as methyl glyoxal have been recalled to be implicated for the glycation reactions [141].

Methyl glyoxal (MG), that is an α-ketoaldehydes, can form in the form of a glycolysis –by product, but is further existing in foods (particularly cooked as well as baked), beverages (mainly those fermented) as well as cigarette smoking, and it is believed to be to commonest robust precursorof AGE generation [142, 143]. Actually, it causes 20,000 times greateras comparedto glucosewith regards to glycation reactions [144]. Over 20 separate AGE's have got isolatedin human tissues. The Ones having maximum significanceare pyrraline, pentosidine, carboxyethyl –lysine (CEL) as well as Methyl glyoxal-lysinedimer (MOLD) [145]. Secondary to MG as well as rest of carbonyl reactivity as well as toxicity, eukaryotic organisms have generated particular enzymes for detoxification. The glyoxalase system actually, is made up of glyoxalases I as well as II in addition to combining with α-ketoaldehydes to GSH for generation of D-hydroxyacids [146]. Rest of the enzymes as well as proteinsaid in counteraction of glycation, like fructosamine-3-kinase catalyses fructosamine phosphorylation which decides protein de glycation [147], as well as aldose reducataseaids in α-oxoaldehyde reaction [148].

Othan diabetic side effects, AGE collection in blood as well as tissues has got linked to a lot of chronic as well as degenerative diseases, like neurodegenerative as well as CVD, atherosclerosis, cancer for stimulatingcell signalling dys function, oxidative stress, as well as inflammation, along with protein accumulation as well as crosslinks [16]. With regards to this AGE collection, oxidative stress, as well as inflammation are linked with the capacity of AGE to bind particular recept or sknown as RAGE. Actually the activation of the AGE pathway has the ability of deregulating gene transcriptions, the signalling among cells as well as the extra cellular matrix (ECM), along with blood proteins, resulting in their binding with RAGE. or macrophages, which in turn, escalates the liberation of growth factors as well as proinflammatory cytokines [149].

RAGE comes from a superfamily of immunoglobilins as well as various tissues like cardiac, vascular pulmonsary as well as brain tissues. Furthermore, their expression, escalates with age, NDD [150, 151]. Despite their being detailed in the form of AGE-binding receptors, multiple other ligands like S100 family molecules, along with high mobility group protein 1, believed to be implicated in inflammation as well as Aβ aggregation events [152].

Once the AGE's as well as rest of the ligands collect, RAGE expression gets generated [153]. as well as elevated amounts have been detailed to stimulate NFκB, that in turn causes enhanced proinflammatory cytokines expression [154]. as well as for the stimulation of MAPK signallingpathwayvia phosphorylation of ERK1/2, p38, as well as JNK, resulting in inflammation, proliferation as well as apoptosis [155]. Further more AGE-RAGE binding results inoxidative stressvia the stimulation of peroxidant NADPH oxidase (NOX2) [156]. Besides RAGE, that binds to AGE, actually AGE1-3 are implicated in the detoxification by binding them on the cell surface as well as controlling the endocytosisfor decreasing oxidative stress, RAGE, as well as inflammation [157]. Significantly, amount AGE Rs get down regulated in a lot of chronic diseases as well as in the presence of large amounts of AGE [158].

That the collection of AGE as well as oxidative stress have a significant, part is well understood inpathogenesis of ND diseases [159]. The brain, inspite of great metabolic rate as well as oxygen utilization, has the properties of poorantioxidant defences. Actually, it has weak expression of antioxidant enzymesalong with low amounts of GSH as well as rest of antioxidants [160]. From these angles brain becomes very vulnerable towards oxidative injury. With thisin mind, it has to be understood that AGE's have a double part, as their generation gets enhanced following oxidative situations as well as since they facilitate oxidative stress [161]. AGE collects has been seen in brains influenced by AD as well as PD along with NDD [162]. Both Aβ plaques as well as NFT present AGE-stimulated protein crosslinks, as well as Aβ aggregation gets exaggerated as well as stabilized once the AGE's are existing [163]. Other than stabilizing Aβ plaques as well as NFT, AGE's have been attributed the role of their generation. That AGE's stimulate APP expression was shown by Ko et al., as well as glycated tau protein stimulated oxidative stress [164]. Further more Aβ is believed to be a RAGE ligand, with binding of Aβ as well as RAGE aiding in disease propagation via stimulation of neuro inflammation as well as oxidative stress [165]. AGE's have been shown to aid further in collection of α-synuclein, a protein that is rich in lysine residues, to generate Lewy bodies, that is a clearcut marker of PD (fig2) [166].

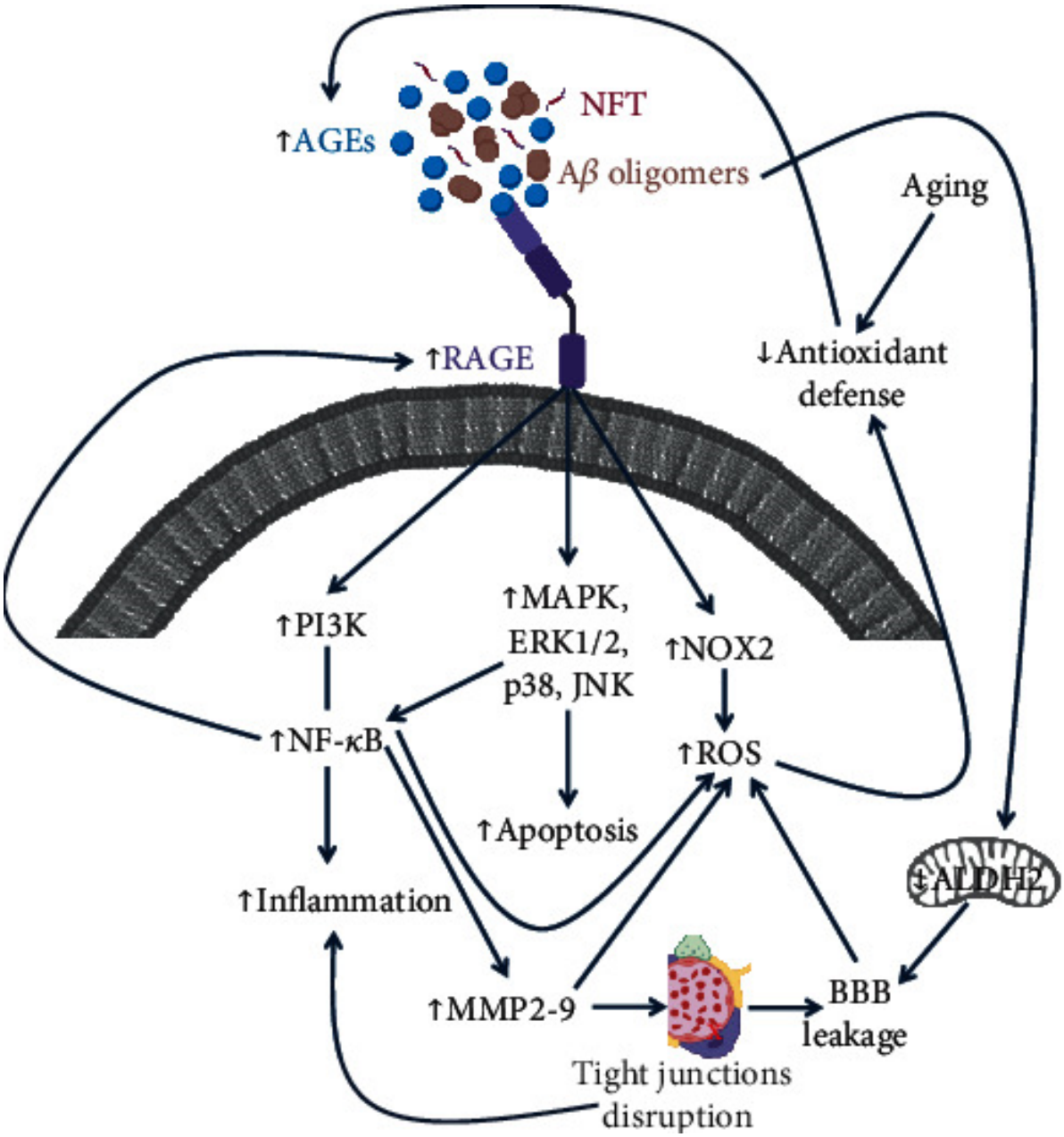

Figure 2: Courtesy refer no-111-The vicious circle of the principal pathways involved in RAGE activation. AGE-RAGE binding activates different signalling pathways, in particular MAPK, PI3K, and NOX2, inducing inflammation, apoptosis, and oxidative stress. Moreover, the increased levels of NF-κB induced the expression of RAGEs. The inflammatory response is also enhanced by the disruption of tight junctions at NVU that compromises also the BBB integrity. Oxidative stress is increased also by the high level of NF-κB and by the consequent increment of MMP2-9. In aging, elevated ROS levels are not efficiently counteracted by endogenous antioxidative defences, and, as a consequence, AGE formation is increased. AGEs not only stabilize Aβ oligomers and NFT but also increase their formation. In addition, Aβ oligomers can also bind RAGE and activate the inflammatory/oxidative cascade. Finally, Aβ oligomers can trigger the impairment of mitochondrial ALDH2, leading to endothelial dysfunction and BBB leakage.

Other than pharmacological strategy ,basically concentrated on targeting rage [165, 168], a natural substanceseems luring. Vitamin B1, that is a coenzyme of transketolase, aids in glycoplytib intermediates that are significant for glycation reaction [168]. Certain flavonoids as well as other polyphenols have been positedas safe candidates for postponing the propagationof AGE-modulated inflammatory diseases [169]. Certain polyphenols-richextracts, like pomegranates, have been shown to inhibit glycation or to trap MG in cell free in vitro systems [170].

Epigallocatechin gallate (EGCG) showed that it influences protective actions in vitro against AGE-toxicity in neuronal cells. Lee as well as Lee demonstrated, in SH-SY5Y cell culture, that 5-10 μM of EGCG therapy suppresses oxidative stress by induction of superoxide dismutase (SOD) as well as Catalase (CAT), reduces MG amounts as well as AGE-generation, along with down regulates RAGE expression [171]. In the in vivo model of rat model of AD, resveratrol (Res) has been detected to decrease RAGE expression at the hippocampal level as well as to influence anti- inflammatory actions as documented by the reduction of NFκB protein expression [172]. Rest of the studies have revealed Resanti- inflammatory characteristics for the induction of sirtuin (SIRT1) protein, as shown by Wangetal. in an in vivo rat model of AD. in SH-SY5Y cell culture, Res therapysuppresses oxidative stress as well as apoptosis stimulated by AGE's [150, 173]. Quertcetin has got revealed to suppressdietary AGE- stimulated cognitive dysfunction in old ICR mice via inhibition of ERK1/2 as well as tau protein phosphorylation [174]. Angeloni et al., showed that sulphoraphane (anisothiocyanate) from Brassica vegetables protects SH-SY5Y neuronal cells

against MG –stimulated injuryby inhibiting the stimulation of caspase-3 enzymes as well as decreasing the phosphorylation of ERK1/2, JNK as well as p38 signalling pathways.

Further more sulphoraphane could suppress oxidative stress to escalate intracellular GSH amounts as well as the expression along with activity ofglyoxalase1[175]. Bioactiveagents obtained from Olea europea, like oleocanthal as well as hydroxyl tyrosol, have the ability to suppress the glycation event [176]. Further more oleocanthal therapy enhances GSH intracellular amounts as well as suppress oxidative stressin neuronal like cell cultures [177]. Aligeloni et al., recently evaluated the, correlation among oleocanthal as well as AD, pointing that other than its actions on influencing tau protein hyper phosphorylation as well as aggregation along with its capacity to stimulate Aβ efflux along with clearance, it might suppress propagation of AD by decreasing glycation in the brain, secondary to its positive effects on GSH amount, besides its ability to decrease oxidative stress [178].

Irrespective of NDD the probability of suppressing the glycation events as well as AGE's toxicity utilizing bioactive agents has recently got confirmedby activators of the Nrf2 signalling pathway have the capacity to stimulate the expression of genes implicated in carbonylstress resistance. Recently it has been shown inthe SH-SY5Y cell culture that the Nrf2 activation bycarnosic acid results in enhanced expression of factors implicated in the GSH generation as well as lets the detoxification of MG viathe glyoxalase system, hence conferring protection on the cells from MG- stimulated carbonyl stress[179].

From these studies, one can posit now that these protective effects of natural bio active molecules against glycation as well as AGE's toxicity might be at least partially, secondary to the manipulation of Nrf2 is the crucial controller of the inflammatory response as well as the oxidative injury associated with neuro degeneration.

Conclusions

Thus it has been visualized that Neuro degenerative diseases tend to have features akin to each other. Despite their properties are not totally well defined, Never the less, oxidative stress, inflammation, excitotoxicity correlated with neuronal loss appear closely linked in both evolution as well as propagation of acute along with chronic situations. In view of the great rate of oxygen utilization as well as low detoxification modes, the brain represent an organ that is significantly exposed to oxidative stress [180]. The complicated structure as well as function still cannot be detailed exactly how neuro degeneration under goes evolution. Their is animmediate requirement for evaluation of the close molecular modes to get insight exactly the way initiation along with propagation of Neuro degenerative diseases is urgent, to be able to fashion greater efficacious treatment aproaches.

Right now, any kind of intervention that can decrease the rate of pathology evolution or even arrest or halt itremainscrucial for treating these kind of pathologies. Any Neuro protective approach that inhibits the inflammatory response along with oxidative stress might manipulatein a positive direction the continuous deterioration of the patients Quality of life (QOL). These Neuro protective approaches might be acting along with synergism with utilizing the endogenous defence, like quenching the generation of the ROS or trying to refashion the antioxidant GSH system along with the associated enzymes, besides decreasing the rate of continuous neuronal death.

Here the complicated network of molecular modes lying behind bothacutealong with chronic neuro degeneration with concentration on the impairment of the redox homeostasis, that acts as the common mode underlying the 5 of the key risk factors namely aging, oxidative stress, inflammation glycation along with vascular damage. Of these aging remains the primary factor that can't be altered, having the properties of significant stress situation which escalates the homeostasis loss, implicating Specifically the immune as well as inflammatory response, that in return escalate oxidative stress as well as developing a vicious cycle [42].

In view of the complicated nature of Neuro degenerative diseases in which multifactorial implication is there, an avoiding approach that might be able to target a lot of risk factors at the same time along with modes in the early stage will be the most appropriate method to slow/arrest the propagation of these Neuro degenerative diseases. Besides utilizing the holistic along with spiritual view towards neuro degeneration with integration of all risk factors would provide further key insightsin our atempt to avoid these Neuro degenerative disorders. In this attempt earlier we have tried to review the role of various monoterpenes, iridoids in treatment of Alzheimers disease, besides resveratrol, quercetin and these natural plant products along with role in blocking the AGE as well as RAGE in case of both T1D as well as T2D that aids in generation of atherosclerosis [181-184]. Further more work has been done on utilization of curcumin like in obesity, besides targetic epigenetic alterations associated with these NDD [185, 186].

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