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Prevention with Synbiosis and Treatment with Thalidomide and Celecoxib for Amyotrophic Lateral Sclerosis

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Abstract: There are a variety of types of amyotrophic lateral sclerosis (ALS). Most patients with ALS (90%) are classified into the sporadic type (SALS) without heredity. 5% of SALS and 3%of familial type (FALS) are caused by mutations in the 43-kDa trans-activating response region DNA-binding protein (TDP-43). 20%of FALS are caused by the mutation of Cu, Zn superoxide dismutase (SOD1). Superoxide dismutases (SODs) catalyze the dismutation which reaction breaks down harmful radicals into non-reactive molecules in the cells. Mutated SOD1 leads to the production of ROS that causes neuronal death. Recently, a number of new causal factors have been found to link to the pathogenesis of ALS. Characteristic pathological mechanism of ALS is the function of cytosolic protein aggregates. Normal cell functions are disturbed in the cytosol and lead to abnormal cellular processes such as oxidative stress, excitotoxicity, mitochondrial dysfunction. Matrix metalloproteinases (MMPs) and Tissue inhibitors of metalloproteinases (TIMPs) process physiological tissue remodeling and pathological conditions, both of which include vascular and fibrotic regenerations, angiogenesis and destructive diseases such as ALS and cancers. The Receptor for Advanced Glycation End Products (RAGE) plays an important role in ALS causing inflammation oxidative stress and cellular dysfunction. RAGE is also expressed in neurons, vascular cells, microglia, and astrocytes in the central nervous system (CNS). β-N-methylamino-L-alanine (BMAA) is a potential environmental factor in ALS, which is derived from the cycad plant synthesized by cyanobacteria. BMAA is consumed mainly as cycad flour. Dysfunction of these factors are closely associated with nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) The drugs that suppress activated NF-κB are currently thalidomide, celecoxib and valproic acid. These drugs might slow down the exacerbation of ALS as they are effective for cancers.

Keywords: Amyotrophic Lateral Sclerosis, Thalidomide, Celecoxib, Valproic Acid, Probiotics

1. Introduction

1.1. Metalloproteinases and Superoxide Dismutase

Superoxide dismutases (SODs) are metalloenzymes consistent of Cu, Zn-SOD, Fe- SOD, Mn-SOD and Ni-SOD found in all living cells. SODs catalyze the dismutation in which the reaction between two identical molecules O_2- into molecular oxygen and hydrogen peroxide (H_2O_2). This reaction breaks down harmful radicals into non-reactive molecules in the cells [1]. 90% cases of ALS are sporadic and without family history, 10% cases are familial and autosomal dominant. Moreover, approximately 20% of familial cases are related to mutated superoxide dismutase 1 (SOD1) gene [2, 3].

Astrocytes and microglia with mutant SOD1 express a variety of pro-inflammatory cytokines through NF-κB, resulting neuroinflammation and motor neuron death in ALS [2, 4].

Endopeptidases are proteolytic hydrolases that catalyze peptide bonds of nonterminal amino acids. Metalloproteinases (MPs) are zinc dependent endopeptidases and degrade a variety of proteins such as collagen and elastin in extracellular matrix (ECM) [5].

MPs play potent roles between cells and ECM leading cell differentiation, proliferation and survival. Tissue remodeling is defined as tissue reorganization that are important for tissue regeneration, would healing, organ development such as muscle and nerves [6, 7]. Matrix metalloproteinases (MMPs) are zinc containing multidomain metalloproteinases and play

an important role in tissue remodeling and degradation of ECM [8]. MMPs were initially classified on substrate specificity into five groups: collagenases, gelatinases, stromelysins, matrilysins, and membrane type [9]. MMP family consists of more than 20 members and 14 are in the vasculature [10].

MMPs process physiological tissue remodeling and pathological conditions, both of which include vascular and fibrotic regenerations, angiogenesis and destructive diseases such as ALS and cancers [11].

Neuromuscular degeneration of ALS is associated with many molecules, especially MMPs and tissue inhibitors of metalloproteinases (TIMPs) play an important role in pathogenesis. MMPs, secreted by many cells including fibroblasts, vascular smooth muscle and leukocytes, act as pericellular proteolysis [12]. It is important to adopt probiotics for oxidative stress, and chemotherapeutic agents that incorporate molecular pathways to NF-κB and, moreover growth factors.

TIMPs are specific and endogenous inhibitors of MMPs that control the function of MMPs in the tissues [13, 14]. In pathophysiological conditions, MMP-9 contributes to the development and wound healing, and also contribute to the immune response that exacerbate disease progression such as immunological diseases and cancers 9 15. MMPs such as MMP-1, 2, 3, and 9 play an important role in the progression of ALS, especially MMP-9 might cause neuromuscular degeneration [16]. MMP-9 has the ability to degrade gelatinase B, therefore, is classified in the gelatinase subgroup 9. MMP-2 and MMP -9 belong to gelatinases group and readily degrade degenerated collagens and gelatins. MMP-9 plays a major role in tissue remodeling such as embryo implantation, neovascularization and immune cell function. MMP-9 expression is closely associated with NF-κB and AP-1 [17].

TIMPs are widely distributed in humans, and specific and endogenous inhibitors of MMPs that control the function of MMPs in the tissues.

TIMPs consist of four TIMPs (TIMP-1, TIMP-2, TIMP-3, and TIMP-4) and inhibit MMPs binding under stoichiometric amount 1:1. The imbalance between MMPs and TIMPs affect the level of MMP activity and derive pathological function of MMPs [13 14].

The drugs that suppress activated NF-κB are currently thalidomide, celecoxib and valproic acid. These drugs might slow down the exacerbation of ALS as they are effective for cancers.

1.2. Receptor for Advanced Glycation End Products (RAGE) and ALS

Age-related dysbiosis are well known and promote inflammation by oxidative stress due to imbalance of GI tract [18]. Skeletal muscle, adipose tissue and the liver are three major targets of insulin because these tissues have overexpressed insulin receptors can deposit and store glucose [19]. About 75% of insulin-dependent postprandial glucose is disposed in the skeletal muscle [20]. Advanced glycation end-products (AGEs) are produced from glucose and proteins with non-enzymic activity in a variety of tissues during aging. AGEs store in various systemic tissues under chronic hyperglycemic circumstances and cause vascular disorders like diabetic vascular complication [21].

Currently dynapenia and sarcopenia are recognized as diabetic vascular complication. AGEs exist intra- and extracellularly and are consistent of proteins, lipids, nucleic acids with complicated structures generate protein fluorescence and cross-linking [22]. AGEs accumulate on proteins especially on the large matrix proteins such as collagen, vitronectin, and laminin through AGE-AGE intermolecular covalent bonds in the extracellular matrix (ECM). These bonds increase stiffness of vasculature. RAGE are activated by AGEs and upregulate NF-κB that promote expression of inflammatory cytokines [23]. Proteins with three aromatic amino acids— phenylalanine, tyrosine, and tryptophan display useful intrinsic fluorescence affecting valuable effect to local microenvironment [24].

AGEs promote oxidative stress, expression of inflammatory cytokines and inflammation. These pathological stimmuli may cause dynapenia and sarcopenia [25].

Accumulation of AGEs and increased cross-linking of collagen have been observed in elderly, resulting in increased muscle stiffness, reduced muscle function [26]. Cross-linking of collagen can be formed by combining with an amino acid having two aldehyde groups composing of difunctional, trifunctional, and tetrafunctional cross-linking structure. Type I collagen is the most abundant fibrillar type collagen in the body playing important role in fibrosis of bone, skin, and connective tissue [27, 28]. Collagen molecule becomes natural collagen polymer [29]. Skeletal muscle is consistent of muscular cells, and connective tissues including tendon, intramuscular connective tissues, ligament and fascia that are associate with muscle amount and strength. Cross-linking of collagen cause sarcopenia (increased muscle stiffness, reduced muscle function) and weakening of tissues with type I collagen such as bone and skin.

The RAGE plays an important role in ALS causing inflammation oxidative stress and cellular dysfunction. RAGE is also expressed in neurons, vascular cells, microglia, and astrocytes in CNS [30].

1.3. Oxidative Stress and Preneoplastic Lesions

Oxidation is associated with molecular signal pathways for normal physiological processes [31]. Oxidative stress is overproduction and accumulation of reactive oxygen species (ROS) in cells and tissues, and damage cells and tissue. In equilibrium state ROS works to detoxify these reactive products like in the case of bactericidal activity of white blood cells [32]. Superoxide radical is a state in which one extra electron is incorporated into a normal oxygen molecule which is unstable and highly reactive leading to cell and tissue damage. ROS is defined as radicals with unpaired electrons in outer orbitals and potent active chemically [33] including superoxide radicals (O_2•−), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and singlet oxygen ($1O_2$). Although most of ROS are produced as by-product of oxygen metabolism, ROS is also produced by environmental factors such as ultraviolet (UV) radiation, pollutants (cigarette

smoking, heavy metals) and xenobiotics [34, 35]. Oxidative stress plays an important role in coexistence of various microbes by the production of a variety of protective enzymes leading to reduce the pathogenic biofilm [36]. There are a variety of intracellular producing factors of ROS such as nicotinamide adenine dinucleotide phosphate (NADPH) LPS oxidase (NOX), mitochondrial electron transport chain leakage, and cytokine receptors. ROS play major roles in initiation and progression of a variety of diseases such as cancer, diabetes mellitus (DM), metabolic disorders, atherosclerosis, and cardiovascular diseases [37, 38].

In human gingival fibroblast study, F. nucleatum inhibits fibroblast proliferation, promotes cell apoptosis, and produces ROS, and inflammatory cytokine partly through AKT/MAPK and NF-κB signaling pathways [39].

It remains unclarified that F. nucleatum induces preneoplastic conditions and contribute to ALS and carcinogenesis. However, F. nucleatum resides in tissues of gastric cancer and adjacent mucosa and the prognosis of patients with Lauren's diffuse type gastric cancer with F. nucleatum-positive is significantly worse [40]. Diffuse type gastric cancer originates from atrophic gastritis and intestinal metaplasia caused by chronic active inflammation. Long-term chronic H. pylori-induced gastric inflammation develops 80% of H. pylori positive atrophic gastritis compared with 10% of H. pylori-negative gastritis [41]. High Fusobacteria abundance in the gastrointestinal tract is associated with microbial translocation in spinal-onset ALS, and also, high oral Fusobacteria abundance is correlated with bulbar-onset ALS [42]. Cyclooxygenase-2 (COX-2) is demonstrated to induce imbalance between cell proliferation and apoptosis and detected in ALS, H. pylori-positive gastritis, and preneoplastic cancerous lesions [43].

1.4. Oxidative Stress and Metalloproteinases

The activity of gut microbiota is regulated by balance of beneficial and harmful microorganism (symbiosis and dysbiosis) [44]. ROS play a harmful role in excess expression [45]. Oxidative stress, elevated intracellular levels of ROS, are released from phagocytic cells such as macrophages, granulocytes, and dendritic cells and play an important role in inflammation and cancers. ROS have adverse effects on DNA causing acute and chronic inflammation resulting in immunological diseases and neoplasm [46, 47]. It is reported that oxidative stress may be an early activator of MMPs in ischemia-reperfusion experiment. Particularly, MMP-9 plays an important role after ischemic stroke to reestablish blood-brain barrier injury and hemorrhagic transformation [48]. HT is the peripheral blood extravasation through a disrupted blood brain barrier into the brain after acute ischemic stroke [49].

1.5. Neuron and Metalloproteinases

Patients with ALS are vulnerable to most motor neurons, however some neurons such as innervating extraocular, pelvic sphincter and slow limb muscles are resistant. Alpha motor neuron (MN) degenerated by ALS is classified into three types of motor units, FF (fast-twitch fatigable), FR (fast-twitch fatigue-resistant), and S (slow-twitch fatigue-resistant) [50]. In ALS, degeneration occurs in the order of FF and FR as the condition progresses, and S is known to be resistant to degeneration. Osteopontin (OPN), also called cytokine Eta-1 is synthesized in a variety of tissues and cells. OPN has a variety of roles including bone resorption, immune cell activation, and ECM remodeling [51].

MMP-9 is expressed in fast motor neurons such as spinal cord, brainstem, and cortex that makes the functions selectively vulnerable. Expressing in fast motor neurons, MMP-9 makes selectively vulnerable to them [52]. Transcription factors play important roles in the regulations of osteopontin and MMP-9 (OPN/MMP-9) expression. The activation of MMP-9 is regulated by NF-κB, which is the therapeutic target in patients with ALS [53]. ECM is degraded synergistically with COX-2 and MMP-9, which might be therapeutic target for COX-2 inhibitor celecoxib with the suppressive activity of activated NF-κB [54]. Neurodegeneration is not only caused by OPN/MMP-9, but also by glial and lymphoid cells in the microenvironment, as it were non-cell autonomous neurodegeneration. Various damages stimulate microglia to release a variety of ROS and proinflammatory cytokines, resulting in dysfunction and death of neurons [55]. There exists a close relationship between immune response and oxidative stress, and elevated and dysregulated ROS production from disease-associated microglia causes neurodegenerative diseases [56]. Activated microglia releases proinflammatory cytokines including IL-1, IL-6, and TNF-α. These factors prevent and promote further inflammatory damage in CNS. Chronic activated macrophage contributes neurodegenerative diseases [57].

1.6. CNS and NF-κB

The NF-κB pathway plays a critical role in immune responses through inflammatory cytokines and could be a novel therapeutic target for ALS [58]. The NF-κB proteins reside in the cytoplasm and regulated by inhibitory proteins such as IκB family members and related proteins with ankyrin repeats, which mediate protein-protein interaction with unique motif [59]. IκBα plays a potent inhibitory role, and p50, p52, p100 and p105 are associated with NF-κB inhibition like IκB. C-terminal potion of these proteins is characterized by the structural resemblance of IκB [59, 60].

NF-κB possess two signal pathways, canonical and noncanonical pathways, both of which are independent and have diverse pathophysiological functions.

The canonical pathway responds to various stimuli leading to IκB degradation by ubiquitin-proteasome system (UPS), which induce nuclear translocation p50/RelA rapidly and transiently [61].

The non-canonical NF-κB pathway activates the RelB/p52 through NF-κB-inducing kinase (NIK). The function of this pathway is slow, persistent and specific and responds to TNF receptor (TNFR) signals. NIK play a key role in the stabilization of the pathway, and deregulated NIK accumulation leads to lymphoid malignancies [62].

It is better to think that the canonical pathway plays a role of stimulatory role in the acute phase and acts temporarily for a short period of time, and noncanonical pathway works slow, persistent and specific in the chronic phase.

Astrocytes and microglia produce the cytokines in the immune systems of CNS [63]. Neuroinflammation is associated with the main neurodegeneration of ALS, which is regulated by NF-κB in spinal cords, which causes extensive astrogliosis, activates microglia, and infiltration of peripheral immune cells leading to neurodegeneration 2 [64].

2. The Role of Stomach Against Microorganism

The acid in the stomach plays an important role in the inactivation of microorganism. Gastric mucosa is prevented from pathogenic bacteria with a chemical barrier gastric acid, that is maintained by homeostasis in gut microbiota. Butyrate is estimated to supply 70% of the total energy of intestinal epithelial cells and prevent imbalance of the cell homeostasis and carcinogenesis [65]. Microbial colonization in the stomach is suppressed by low gastric pH (pH<3, 15 minutes) [66]. Gastric juice or Gastric acid is a digestive fluid of HCl, lipase, and pepsin, which play a key role in digestion of lipid and proteins [67, 68].

Local hormone secretin is expressed from S cells of intestinal glands. Greater amount of secretin is released with lower pH. Secretin prohibits the formation of HCl and stimulate gastric pepsin secretion [69].

β-N-methylamino-L-alanine (BMAA) is bacterial neurotoxin produced by cyanobacteria, which is estimated to be the etiology of ALS [70-72]. Chronic exposure to BMAA leads to neurodegenerative condition such as ALS through low grade gut inflammation caused by pro-inflammatory such as IL-8, IL-6, and triggering receptor expressed on myeloid cells 2 (TREM2) [73]. Cyanobacterial extract helps the growth of H. pylori [74].

H. pylori expresses oxidative stress such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) leads to chronic inflammation, DNA damage and cancer initiation [75]. H. pylori leads to chronic inflammatory response secreting proinflammatory mediators such as IL-1β, IL-6, IL-12, TNF-α and interferon (IFN)-γ persistent throughout life. These factors cause neuroinflammation and finally neurodegenerative disease like ALS [76, 77].

The first line chemotherapy of H. pylori is triple therapy with two antibiotics and a proton-pomp inhibitor. However, it is reported that H. pylori disappears gradually with the change of human gut microbiota [78, 79].

3. Bibliographic Reviews: Thalidomide, Celecoxib and Valproic Acid for ALS

Glutamic acid plays an important role as an excitatory neurotransmitter, however it is cytotoxic with excess amount. Hyperactivation of glutamate receptors lead to excessive calcium ion influx, resulting in activation of calcium-dependent enzymes, mitochondrial dysfunction, and apoptosis [80, 81].

The pathological cell degradation in ALS is associated with excitotoxicity, oxidative damage, and apoptosis. Cyclooxygenase-2 stimulate the production of prostaglandin E2 (PGE2), which release glutamate from astrocyte. COX-2 also releases proinflammatory cytokines, ROS and active radicals [82].

COX-2 and PGE2 are upregulated also in microglia through the activation of MAPK/ERK pathway and initiate the same features in astrocyte [83]. The COX-2 inhibitor, celecoxib, significantly reduces astrogliosis and microglial activation 84.

Thalidomide with the anti-inflammatory and immunomodulatory properties protect neuron degradations and reduce astrogliosis and microgliosis [84].

Although the effect of valproic acid (VPA) has not been determined, there are reports that significant prolongation of life with patients with ALS has been shown, and can be used for a long period of time with good tolerance and safety. However, there are some questions on the evaluation. It will be important to bring out the effect of histone deacetylase (HDAC) inhibitors in combination with thalidomide and celecoxib [85-87].

4. Treatment

ALS is neurodegenerative disease of upper and lower motor neurons that generally fatal within a few years after diagnosis. Although no curative treatment is reported on articles, it may be possible to use the drugs that suppress activated or irregulated NF-κB.

The combination of immunomodulatory agents in ALS is superior to best supportive care and might prolong survival. In the setting of immunomodulatory agents, thalidomide, celecoxib and valproic acid that suppress activated NF-κB through non-canonical signal pathway may be more effective.

Monoclonal antibodies act on receptors outside of the cells. However, no growing body of evidence supports that the signal reach transcriptional factors that suppress activated NF-κB [88].

Table 1. *Drugs and molecular targets.*

Figure	Receptor	signal transduction	transcriptional factor	chromatin	molecular target	ref
Thalidomide			NF-Kb		＊α-syn	89
Celecoxib			NF-κB COX-2		COX-2	90
Valproic acid				HDACs		85
＊alpha-synuclein						

Neuroinflammation, activated in glial cells, lead to neurodegeneration in ALS.

Short-chain fatty acids (SCFAs) (e.g., acetate, propionate, butyrate) with anti-inflammatory activity is produced in colon from the fermentation of indigestible fiber. Butyrate plays a potential role in the progression and therapeutic reagent of ALS [91-93].

4.1. Probiotics

Beneficial gut microbiota such as Bifidobacterium and Lactobacillus acidophilus promote immune responses mainly through metabolites including SCFAs, flavonoids and glucosinolates (isothiocyanates) 44 [94]. SCFAs are the main metabolites of dietary fibers and resistant starch in the colon [95].

F. nucleatum expresses ROS, RNS and LPS, sequently next, proinflammatory cytokines are released 44. F. nucleatum is able to form biofilms to protect from surrounding microenvironment, increasing the formation of biofilm in response to alkaline pH [96, 97].

The pH of atrophic gastritis is generally higher than pH ≥3 67 [98].

4.2. Berberine

Berberine is derived from Phellodendron amurense. It is used in the management of diarrhea and is nontoxic in human normal cells. Berberine is anti-inflammatory agent [99-101]. Berberine down-regulates the cytokines expression. The protein quality control (PQC) system regulates proteostasis through protein folding and degradation. Androgen receptor with elongated polyglutamine (polyQ) tract (ARpolyQ) is a mediator for neuromuscular degeneration in spinal and bulbar muscular atrophy (SBMA) caused by SOD1 [102-104]. Berberine clear the misfolded proteins SOD1 responsible for ALS and might be the therapeutic tool [105-107].

4.3. Thalidomide and Celecoxib

Thalidomide is prescribed an immunomodulatory drug. It is used as mRNA encoding inhibitor such as VEGF and TNF-α. Pro-inflammatory cytokines expression is inhibited by Thalidomide through modulating activated or irregulated NF-κB within the CNS [108].

COX-2 is constitutively overexpressed in chronic inflammatory pathogenic mediator in ALS. COX-2, upregulated in spinal astrocytes and neurons, catalyzes PGE2, by which stimulates glutamate expression. COX-2, upregulated in spinal astrocytes and neurons, catalyzes PGE2, by which stimulates glutamate expression 82 [109]. COX-2 inhibitor celecoxib suppresses the expression of pro-inflammatory cytokines, ROS and active radicals. Symptoms of ALS such as neuromuscular weakness and weight loss could be decreased and prolong survival [84].

4.4. Valproic Acid (VPA)

VPA is prescribed in the treatment of convulsion. Nowadays, it is being used in the management of ALS [110]. It works as HDAC inhibitor and sometimes VPA and immunomodulatory drugs are used to treat ALS.

Long usage of VPA exerts neuroprotective effects with epigenetic alterations in a variety of intracellular signaling pathways [85].

5. Conclusion

5.1. For Mild ALS

Management and Prevention of ALS is to inhibit pathogens binding to Toll-like receptor 4, and to choose the drugs that works on transcriptional factors such as NF-κB [111].

1. Probiotics + berberine (100-300mg/day p.o) every day
2. Celecoxib (400mg/day) + Valproic acid (600mg/day) every day

5.2. For Moderate ALS

1. Probiotics + berberine (100-300mg/day p.o) every day
2. Celecoxib (400mg/day) +Valproic acid (600mg/day) every day
3. Thalidomide (50-100mg/day) every day

5.3. For Severe ALS

1. Probiotics + berberine (100-300mg/day p.o) every day
2. Celecoxib (400mg/day) +Valproic acid (600mg/day) every day
3. Thalidomide (200mg/day) every day

There are many side effects in thalidomide use such as birth defects and peripheral neuropathy. It is important to use thalidomide from low dose and not to use it who will be pregnant couple.

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