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Implications of Hydrogen Sulfide in Epigenetic Controlling in Neurodegenerative Diseases: A Narrative Review

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Review Article

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Abstract

Previously we had we have reviewed various neurodegenerative diseases (NDD), inclusive of Alzheimer's disease (AD), Parkinson's disease (PD), as well as Huntington's disease (HD), role of hydrogen sulfide (H_2S), in treatment of different cancers inclusive of breast cancer, glioma, hepatocellular carcinoma along with role of epigenetics in Diabetic Kidney Disease (DKD), as well as pregnancy. There by the objective of this review is provision of an exhaustive outline of the present research controlling epigenetic events correlated with NDD. Here we conducted a narrative review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like neurodegenerative diseases (NDD); Alzheimer's disease ; H_2S Parkinson's disease; Huntington's disease; hydrogen sulfide; Epigenetics; DNA methylation; Histone post-translational modifications; Histone protein acetylation; Histone methylation from 2000 till 2023 December till date. Emerging proof has initiated the unravelling of various facets by which H_2S impacts the epigenetic topography along with followed by the propagation of different NDD inclusive of AD, PD), as well as HD. H_2S possesses the capacity of modulating the crucial epigenetic machinery for instance DNA methylation, histone modifications along with noncoding RNAs influencing gene expression as well as cellular working germane to neuronal survival, neuroinflammation, as well as synaptic plasticity. Thus it is constructed how H_2S works in the form of an imperative actor amongst this close-knit network possessing the probability of opening innovative therapeutic arena. Although considerable work done, still lot of lacunae exist on the exact molecular modes plausible therapeutic repercussions of modulating the H2S quantities/its downstream targets. Finally isolation of future research directions having the objective of using the therapeutic capacity of H_2S in NDD.

Keywords: Neurodegenerative Diseases (Ndd); Epigenetic Modifications; Hydrogen Sulfide (H_2S); Alzheimer's disease (AD); Parkinson's Disease (PD); Huntington's Disease(HD)

Abbreviations: HAT's: Histone Acetylases; CPG: Cytosine-Phosphate-Guanine; OS: Oxidative Stress; SAM: S-Adenosyll Methionine; NFT: Neurofibrillary Tangles; BACE 1: Beta Site Amyloid Precursor Protein Cleaving Enzyme; CNS: Central Nervous System; QOL: Quality of Life; DNMT: DNA Methyltransferases; ROS: Reactive Oxygen Species; DKD:

Diabetic Kidney Disease; NDD: Neurodegenerative Diseases; CSE: Cystathionine-Gamma-Lyase; PD: Parkinson's Disease; HD: Huntington's Disease.

Introduction

Tackling neurodegenerative diseases (NDD), inclusive of Alzheimer's disease, Parkinson's disease as well as Huntington's disease are considerably difficult in the modern medicine [1]. These situations possess the properties of continuous irreversible elimination of neurons which result in reduction in the cognitive in addition to motor working [2]. They have assumed a substantial important position in the form of a subset of non-communicable disease, accelerated by our prolonged life period of human life as well as [3] influencing the lives of millions of people world over. Apart from resulting in emotional suffering, they further have a considerable cost wise burden over the society [4].

Trying to explore the biology of these complicated situations displays a close web of etiological factors implicated in a complicated crosstalk of genetic, epigenetic in addition to environmental factors which together guide the initiation as well as propagation [5]. Of these factors, epigenetic alterations have become key deciders in the formation along with the path followed by the NDD [6].

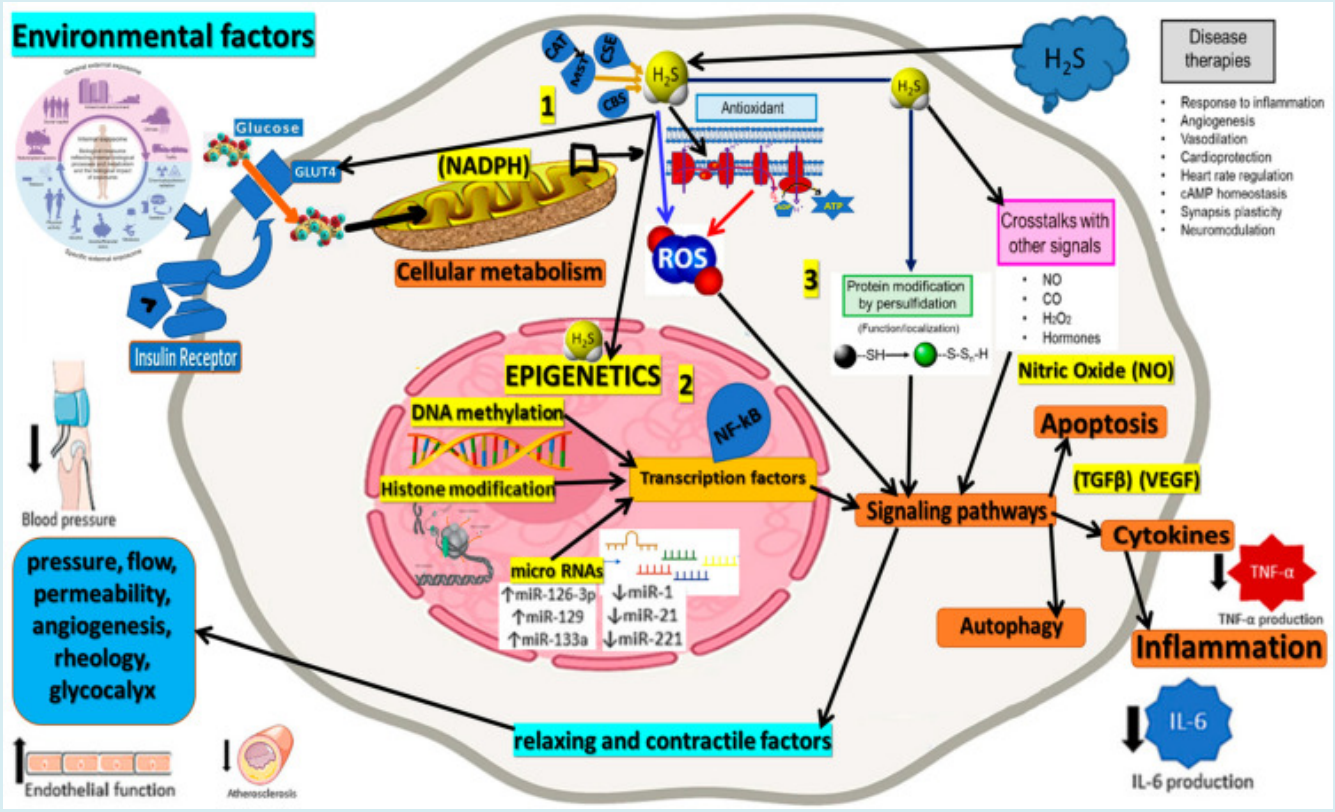

Figure 1: Inuzuka H, et al. [38]- This figure illustrates the central role of Hydrogen Sulfide (H_2S) in epigenetic regulation and its interactions with various processes associated with neurodegenerative diseases. H_2S affects epigenetic mechanisms, including histone modification, DNA methylation, and non-coding RNAs, which modulate gene expression and cellular functions relevant to neurodegeneration. H_2S influences reactive oxygen species (ROS) production and oxidative stress levels, which play a critical role in the pathogenesis of neurodegenerative disorders. By reducing ROS production (blue arrow) and inhibiting ROS-generating processes at the mitochondrial level (red arrows), H_2S impacts a broad spectrum of biological functions, as depicted in this figure for illustrative purposes. The interplay between H_2S, epigenetic processes, and oxidative stress offers valuable insights into the molecular mechanisms underlying neurodegeneration and highlights the potential for therapeutic interventions to restore epigenetic balance and mitigate oxidative stress to combat neurodegenerative diseases effectively. The figure corroborates 3 major parts: 1: External sources and internal production of H_2S; 2: The epigenetic role of H_2S; and 3: The physiological connections presented in a simplified way.

Epigenetic modes possess an elemental part in gene controlling promoting dynamic alterations in gene actions without changing the basic sequence of DNA [7-9]. Epigenetics is inclusive of DNA methylation, Histone modifications in addition to the noncoding RNAs (nc RNAs) [10-12]. Further than this biological significance, epigenetic alterations further give an evolutionary [13]. Modifications of the gene actions in reactions to environmental clues without changing the sequence of DNA gives provision to organisms with a considerable benefit [14]. Probably this has aided all the living organisms with regard to adaptation along with flourish in variable environments [15]. Although hydrogen sulfide (H_2S), has been believed to be correlated with being a toxic gas possessing rotten egg odour in addition to plausibly correlated with toxicity at greater quantities. H_2S, has been illustrated to be a promising molecule for evaluation of numerous physiological as well as pathological events [16,17]. Endogenous hydrogen sulfide generation takes place in the brain via the enzymatic degradation of cysteine by cystathionine-beta-synthase (CBS), cystathionine-gamma-lyase (CSE), in addition to 3 mercaptopyruvate sulfurtransferase (3-MPST) [16]. Its working is in the form of a neuromodulator along with has been illustrated to possess a key part in controlling synaptic transmission, survival of neurons, as well as neuroinflammation) [17].

Recent corroboration points that H_2S might be cross talking with different epigenetic modes implicated in the generation of NDD [18-60]. By impacting epigenetic alterations H_2S might influence gene expression designs germane to these diseases. This probable crosstalk amongst H_2S along with epigenetic panorama yields a newer outlook towards our gaining insight with regards to these complicated situations as well as emphasizes the requirement of future research evaluating the part of the H_2S in addition to mode of these diseases [19].

Previously we had we have reviewed various neurodegenerative diseases (NDD), inclusive of Alzheimer's disease, Parkinson's disease as well as Huntington's disease, role of H_2S in treatment of different cancers inclusive of breast cancer, glioma, hepatocellular carcinoma along with role of epigenetics in Diabetic Kidney Disease (DKD), as well as pregnancy [18-37].

There by the objective of this review is provision of an exhaustive outline of the present research controlling epigenetic events correlated with NDD (Figure1) [38].

Methods

Here we conducted a narrative review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like neurodegenerative diseases (NDD); Alzheimer's disease; H_2S Parkinson's disease; Huntington's disease; Hydrogen Sulfide ; Epigenetics; DNA Methylation; Histone Modifications; Histone Protein Acetylation; Histone Methylation from 2000 till 2023 December till date.

Results

We found a total of 300 articles out of which we selected 97 articles for this review. No meta-analysis was done.

Role of Hydrogen Sulfide

Of the part of the crucial modes controlled by H_2S are histone modifications. H_2S has been illustrated to result in modifications of the histone proteins via sulfhydration, an event by which addition of sulfur atom takes place in the particular histone cysteine residues [15]. Sulfhydration of histone possess the capacity of manipulation of the chromatin structure in addition to gene expression, finally impacting different cellular events. For example, H_2S modulated histone sulfhydration has been revealed to influence the gene expression implicated in synaptic plasticity , memory generation as well as survival of the neurons [39]. Decontrolling of this event has been held responsible in the pathogenesis of NDD [40], inclusive of Alzheimer'sdisease(AD) [41], Parkinson's disease(PD) as well as Huntington's disease.

DNA methylation portrays one more key epigenetic mode impacted by H_2S [42]. DNA methylation implicates adding a methyl group to the cytosine residues on CpG dinucleotide, resulting in transcriptional suppression of target genes. H_2S has been illustrated to control the actions of DNA methyltransferases (DNMT), the enzyme implicated in DNA methylation. Alterations in DNMT action in view of H_2S decontrolling have been correlated with changed DNA methylation designs in the neurons, aiding in the abnormal gene expression found in NDD. For example H_2S modulated alteration in DNA methylation have been correlated with the decontrolling of genes implicated in the neuroinflammation, oxidative stress (OS), in addition to survival of neurons [43].

Apart from histone modifications along with DNA methylation, H_2S crosstalks with nc RNAs inclusive of microRNAs (miRNAs), long noncoding RNAs (lnc RNAs) [44]. MiRNAs represent small nc RNAs which post transcriptionally control gene expression by targeting mRNAs for breakdown or translational suppression. The decontrolling of miRNAs has been held responsible in different kinds of neurodegeneration inclusive of protein clustering, neuroinflammation as well as synaptic impairment. H_2S has been illustrated to modulate the expression of in addition to actions of the particular miRNAs resulting in changed gene

expression profiles in the neurons [45].

Moreover lnc RNAs, which portray a class of nc RNAs longer than 200 nucleotides, have further been observed to possess a key part in the neurodegenerative events. H_2S possesses the capacity of impacting the expression along with the working of the lnc RNAs, thus influencing gene expression in addition to cellular events in neurons. Decontrolling of particular lnc RNAs have been correlated with NDD, as well as their crosstalk with H_2S further reemphasizes the importance of epigenetic controlling of the neurodegeneration [46].

Hydrogen Sulfide Along with Neurodegenerative Diseases (NDD)

Hydrogen sulfide (H_2S), portrays a gasotransmitter, a gas molecule that is existent naturally in case of organisms as well as has received recognition for the plethora of parts it possesses in physiological along with pathological events [47]. H_2S has managed to invoke so much attention in biology although it is correlated with possessing rotten egg odour [48,49]. H_2S has been observed to impact neuroinflammation , OS in addition to mitochondrial impairment in case of NDD. Its importance in neurodegeneration is an interesting field of assessment, with the plausibility of displaying innovative therapeutic approaches [17,50]. By akin approach for the assessment of H_2S with regard to evolution as well as epigenetics, a greater insight of its complicated pathophysiology gets derived [15,51].

This scientific team evaluation emphasizes the significance of interdisciplinary work which results in connection of evolutionary biology with the molecular medicine that might be contributing in the generation of the enhancement of treatment in addition to quality of life (QOL) for the subjects suffering from NDD along with the probability of the other health situations.

In case of central nervous system (CNS), H_2S controls vasodilatation, confers protection against OS stimulated injury along with modulates inflammatory reactions, key for sustenance of the neuronal health in addition to proper working of the brain [52]. H_2S further impacts appropriate working of the immune system as well as facilitating immune balance [53]. Nevertheless, controlling of the quantities of the H_2S intricately is imperative in view of greater quantities possess toxicity, resulting in cellular injury along with demise [17,54]. Enzymes for instance CBS, CSE, in addition to -MPST control H_2S quantities for avoidance of the inimical accrual, while aiding in its advantageous working of the signalling [50,55]. Asssessment of H_2S in biology is with regards to evolution, pointing that its part has been evolutionary preserved in cellular events contributing to aid organisms in adaptation to the altering milieu in addition to tackling the environmental hurdles, thereby impacting gene expression as well as cellular working in different manners [32,56].

In case of AD H_2S has been illustrated to modulate the actions of the enzymes responsible for the generation of the amyloid beta (Aβ) in addition to tau protein phosphorylation,key events in the pathogenesis of AD [17,57]. In particular H_2S possesses the capacity of facilitating the formation of Aβ via its impact on the enzyme Beta site amyloid precursor protein cleaving enzyme (BACE 1) alias β-secretase (BACE1) along with the γ-secretase complex [58]. Furthermore H_2S has been illustrated to result in tau phosphorylation, resulting in the collection of hyperphosphorylated tau into neurofibrillary tangles (NFT) [59]. Moreover H_2S possesses the capacity of aiding in neuroinflammation, in addition to OS, aggravating neurodegeneration in AD [60].

With regards to Parkinson's disease (PD) existence in neurons of α-synclein (α-syn) protein collections generating inclusion bodies known as Lewis bodies portrays the central characteristics of this disease [61]. H_2S has been believed to be responsible for the assembly along with misfolding of the α-syn, facilitating its neurotoxicity in addition to aiding in the propagation of PD. Furthermore, H_2S possesses the capacity of impacting mitochondrial working as well as stimulating OS, both correlated with dopaminergic neuronal demise in case of PD [62]. H_2S stimulated inflammation as well as microglial activation might further impact the propagation of the disease pathogenesis [62,63].

In case of Huntington's disease (HD) accrual of mutant huntingtin protein correlated with expansion of CAG((cytosine adenine guanine)/ polyglutamine repeats in the exon 1 of huntingtin gene on chromosome 4 is key in the disease event [64]. H2S has been illustrated to impact the collections along with the toxicity of the mutant huntingtin, aiding in the neurodegeneration of the neurons in the striatum in addition to other regions of the brain influenced in the HD. Furthermore, H_2S possesses the capacity of mitochondrial impairment along with OS, further aiding in neuronal injury in HD [65,66].

Additionally, the current work points that H_2S might be involved in the decontrolling of autophagy,a cellular event key for elimination of misfolded proteins in addition to injured organelles. Decontrolling of autophagy has been believed to be involved in the pathogenesis of the NDD, as well as H_2S might be aiding in dysfunctional autophagy in these situations [67]. Despite, the appropriate modes by which H_2S impacts NDD are still getting evaluated, the current work validates apart from emphasizing its probable attractive part in the form of a therapeutic target.

Epigenetic Controlling of Neurodegenerative Diseases (NDD)

Epigenetic controlling possesses a key part in the pathogenesis of the NDD, impacting gene expression as well as cellular working germane to neuronal health [68]. Epigenetics portrays modifications which take place on the genome without changing the DNA sequence lying beneath , in addition to these alterations might be inherited or impacted by environmental factors. In case of NDD decontrolling of epigenetic modes has been believed to be involved in the interference with normal cellular events in addition to propagating elimination of neurons [7,69].

Chromatin remodelling is elemental epigenetic modes which control gene expression by manipulation of the chromatin structure constituted of DNA along with the histone proteins [70]. ATP based chromatin remodelling complexes possess the capacity of decontrolling of key genes implicated in the neuron survival in addition to working [71]. Furthermore, histone modifications for instance acetylation in addition to methylation dynamically controls gene expression in case of neuron, as well as their disturbances have been found in different neurodegenerative disorders [72]. These epigenetic changes in chromatin remodelling possess the capacity of influencing the expression of the gene correlated with disease pathology emphasizing the importance of chromatin remodelling in neurodegeneration [73]. Targeting the chromatin remodelling factor might be an attractive strategy for generation of the epigenetic dependent treatment for avoidance of NDD propagation in addition to facilitating neuroprotection. Greater requirement of scientific research exists to get insight about the molecular modes as well as the plausible therapeutic repercussions of chromatin remodelling in NDD [12].

Three primary epigenetic modes are specifically germane to neurodegeneration: i) DNA Methylation; ii) Histone Modifications as well as; iii) Noncoding RNAs (nc RNAs) [10].

i. DNA Methylation

DNA methylation refers to an enzymatic event which implicates the covalent transfer of methyl (CH3) group from S-adenosylL methionine (SAM)to the 5-carbon of cytosine residues which canonically takes place specifically at on cytosine-phosphate- guanine (CpG) regions [74,75]. Methylation of the CpG islands (80-1000nucleotides) mainly, the ones existing on the gene promoter or in the 1st exons is correlated with gene silencing, resulting in reduction of the gene expression . In case of NDD abnormal DNA methylation designs have been found in genes having a key part in neuronal working, for instance synaptic plasticity, neuroinflammation, oxidative stress (OS) reactions, survival of the neurons. These alterations in case of DNA methylation possess the capacity of influencing gene expression correlated with pathogenesis of disease, aiding in the impairment along with the demise of neurons [75].

Escalation of research has been aiding in acquisition of insight over the dynamic kinds of DNA methylation in case of neurodegenerative conditions in addition to its influence over propagation of disease [76]. For example neurodegenerative conditions studies have illustrated changed DNA methylation designs in case of genes correlated with amyloid beta (Aβ) processing in addition to tau phosphorylation in AD [77]. Akin to that in case of PD decontrolled abnormal DNA methylation designs have been found in genes correlated with mitochondrial working, dopamine signaling along with neuroinflammation [78,79].

Furthermore DNA methylation alteration, have been involved in controlling genes correlated with reactions to OS, an event intricately associated with neurodegeneration. OS stimulated DNA methylation changes possess the capacity of impacting the expression of genes correlated with antioxidant defense, accelerating neuronal susceptibility to oxidative injury [80].

With the recent advancements with regards to epigenomic technologies for instance genome wide DNA methylation profiling have yielded remarkable understanding into particular pathways influenced by DNA methylation alterations in case of NDD [74].

ii. Histone Modifications

Histones portray proteins around which DNA wrapping takes place for the generation of chromatin,a complicated structure implicated in the packaging of the DNA into the nucleus. Histone modifications for instance acetylation, methylation, phosphorylation, ubiquitination possess the capacity of changing the availability of the DNA to the transcriptional machinery, impacting the expression of genes. Decontrolling of histone modifications has been thought to be responsible for NDD, resulting in changed genes expression designs which might be aiding in disease propagation. For instance histone deacetylales (HDACs) , enzymes implicated in histone deacetylation have been illustrated to control gene expression in case of AD in addition to HD [81].

Regarding AD interference with histone acetylation in addition to histone deacetylation events have been associated with the pathology of the disease. HDACs, a class of enzymes responsible for deacetylation possesses a key part in the controlling of the genes expression in case of AD [73]. Different studies have illustrated that decontrolling of particular HDACs for instance HDAC2 is correlated with synaptic impairment as well as cognitive dysfunction in case

of AD. Furthermore, Histone acetylases (HAT's), the enzymes implicated for acetylation are involved in the pathogenesis of AD. HAT's being implicated in the histone acetylation, have been believed to be responsible for resulting in a relaxation of the chromatin structure as well as elevated transcription of genes. Noticeably, the decontrolling of the HAT's might be aiding in the changed genes expression implicated in neuroinflammation along with the processing of the amyloid beta(Aβ) [72].

Additionally, histone modifications have been associated with the other NDD, for instance PD [82]. Changed quantities of the histone acetylation have been correlated with mitochondrial impairment in addition to OS, aiding in the neuronal degeneration of the dopaminergic neurons in the substantia nigra pars compacta (SNc) [83]. Furthermore, histone methylation designs have been displayed to control α-synclein(α-syn) expression,a protein responsible for the pathogenesis of PD [18].

HD, portrays an inherited neurodegenerative conditions, where histone modifications have further been thought to be responsible for the pathophysiology of the disease. For example, abnormal histone methylation designs have been found in case of HD resulting in genes expression correlated with neuronal impairment. Additionally, HDAC hampering agents have been illustrated to possess actions in the preclinical models of HD, pointing to the probability of therapeutic targeting histone modifications in this condition [84].

iii. Noncoding RNAs (nc RNAs)

Noncoding RNAs (nc RNAs) represent RNAs molecule which do not code proteins however possess controlled working in the cell. Two main kinds of nc RNAs implicated in epigenetic controlling are microRNAs (miRNAs) as well as long noncoding RNAs (lnc RNAs).

MiRNAs represent small RNAs molecules possessing the capacity of binding to the target messenger RNAs (mRNA) resulting in mRNA breakdown or -translational suppression. The decontrolling of the miRNAs has been correlated with NDD. Abnormal expression of the particular miRNAs possess the capacity of interfering with crucial pathways associated with neuroinflammation, synaptic plasticity, along with mitochondrial working aiding in the pathogenesis of NDD.

Conversely lnc RNAs portray a variable group of the transcripts which are longer than 200 nucleotides in addition to do not encode proteins [85]. Lnc RNAs possess the capacity of cross talking with the chromatin modifying complexes, impacting genes expression by epigenetic modes. Changed expression of the lnc RNAs has been correlated with neurodegenerative conditions, aiding in the decontrolling of the gene expression as well as cellular working [86].

Collections of proof has displayed the key part of the lnc RNAs in the form of epigenetic controllers, working in the form of scaffolds for the chromatin modifying complexes crosstalking with different epigenetic controllers for impacting genes expression [87].

In case of NDD changed expression of the lnc RNAs has been correlated with decontrolled gene expression designs in addition to cellular working impairment [88]. For example certain lnc RNAs have been observed to crosstalk with the histone modifying enzymes for instance histone methyltransferases (HMTs), or demethylates resulting in the alterations in histone methylation designs followed by transcriptional changes [25].

Moreover lnc RNAs possess the capacity of working in the form of competing endogenous RNAs (ce RNAs) by competitively binding to the miRNAs,thus modulating the accessiblity of the miRNAs to the target mRNAs. This kinds of ce RNAs interactions might be possessing crucial part with regards to fine tuning of the gene expression networks with regards to neurodegeneration [89].

Decontrolled lnc RNAs-miRNAs crosstalking has been displayed in NDD in addition to their actions on the target gene expression might be implicated in the neuronal survival, in neuroinflammation, as well as protein collections [90].

Furthermore, recent studies have emphasized how the circular RNAs (cir-c RNAs) are implicated in the NDD. Cir-RNAs represent a distinct class of the nc RNAs possessing covalently closed circularstructures. They have been illustrated to control gene expression by crosstalking with the miRNAs or RNA binding proteins in addition to their decontroling has been thought to be responsible in the pathogenesis of the neurodegenerative conditions [91].

Thereby the dynamic kinds of epigenetic modifications yield probability of taking therapeutic actions, in view of these alterations being reversible. Targeting these epigenetic modes is attractive for the generation of the innovative treatment regarding modifications of disease propagation in addition to enhancement of the results in case of subjects afflicted by NDD. Nevertheless, an exhaustive insight regarding the particular epigenetic alterations as well as their functional outcomes in case of neurodegenerative conditions continues to be a significant field for researchers. Unfolding the mysteries of the epigenetic controlling of these diseases might be aiding in the isolation of biomarkers in addition to innovative therapeutic targets, finally provision of hope for giving greater efficacious treatments in future [76,92].

Acknowledging the complicated aspect of NDD inclusive of AD, PD in addition to HD,clarity is there regarding

epigenetic controling possesses a significant part in the propagation of the disease. The close crosstalk amongst genetic, environmental along with the epigenetic factors aid in the elimination of neurons found in these conditions.

H_2S has been observed to crosstalk with the variable epigenetic modes, impacting gene expression in addition to cellular working germane to neuronal health. By cross talking with epigenetic controllers for instance DNA methylation, histone modifications as well as noncoding RNAs (nc RNAs), H_2S possesses the capacity of impacting gene expression, key for neuronal working as well as survival [5,93].

H_2S along with DNA Methylation

DNA methylation modulation by the H_2S portrays an intriguing crosstalk amongst this gasotransmitter in addition to epigenetic controllers regarding NDD. Different studies have illustrated that H_2S possesses the capacity of modulating DNA methylation designs by influencing the actions of the enzymes implicated in the DNA methylation for instance DNA methyltransferases (DNMT) .Like H_2S has been observed to be hampering DNMT actions, leading to reduction of the DNA methylation at the particular gene promoter areas.This diminished methylation can result in changed gene expression , plausibly influencing pathways key for neuronal survival, neuroinflammation as well as OS reaction. Furthermore, H2S has been observed to impact the gene expression in controlling H_2S metabolism, generating a feedback loop which further influences the epigenetic panorama. This close knit crosstalk amongst H_2S along with DNA methylation emphasizes the plausible significance of the epigenetic modes in the pathogenesis of neurodegenerative conditions, yielding innovative arena regarding therapeutic targeting H_2S modulated epigenetic decontrolling. Greater work might be unravelling the total degree of the H_2S part regarding shaping epigenetic topography in addition to its repercussion for NDD propagation as well as plausible treatment approaches [51,94].

H_2S Along with Histone Modifications

H_2S works on the histones via crosstalk with the histone modifying enzymes which influences acetylation, methylation, as well as phosphorylation. By impacting such histone modifications H_2S possess the capacity of changing the availability of the DNA to the transcriptional machinery resulting in alterations in the expression designs. Noticeably, H_2S has been illustrated to influence the actions of the HAT's in addition to HDACs,namely the enzymes implicated in the histone acetylation that possess a key part in the controlling of the gene expression in case of NDD. Decontroling of the histone modifications by H_2S might be aiding in the changed gene expression of the genes correlated with neuroinflammation, neuroprotection in addition to other events implicated in neurodegeneration. Greater assessment into the particular crosstalk amongst H_2S as well as histone modifying enzymes would thus be key in unveiling the complicated modes behind H_2S modulated epigenetic controlling regarding NDD generation, plausibly resulting in the generation of the innovative epigenetic dependent treatments of NDD [15,49,95].

H_2S Along with Noncoding RNAs

H_2S has been illustrated to modulate the expression of the particular miRNAs in addition to the lnc RNAs which possess the controlling of the gene expression. By impacting the quantities of the nc RNAs H_2S has the capacity of influencing the stability of the mRNAs as well as protein translation, resulting in alteration in the cellular working. Decontroling of the miRNAs in addition to the lnc RNAs has been found in the NDD along with the crosstalk amongst H_2S along with these nc RNAs might be aiding in the pathogenesis of the disease [95].

Further Evaluation & Future Research Directions

Future research would thus be key regarding advancements of plausibility of H_2S dependent treatments regarding NDD, giving greater hope for subjects challenged with these debilitating conditions. For attainment of these aims, variable key regions need evaluation i) to perform asssessment of appropriate molecular modes via which H_2S crosstalk amongst epigenetic controlling in addition to cellular pathways takes place in case of neurodegeneration is necessary for acquisition of insight regarding its neuroprotection as well as the therapeutic clinical repercussions ii) exhaustive studies evaluating long term safety along with effectiveness are imperative prior to thetranslation of H_2S dependent treatments in clinical scenario. Acquisition of insight about plausible inimical sequelae, dose reaction association as well as actions on the cellular events would thus guarantee the safety along with efficacy iii) it becomes key to isolate ideal delivery approaches for the H_2S dependent treatments taking into account their bioavailability in addition to tissue spread in the variable routes of delivery for different stages of the disease along with the patients population. Moreover, targeted scientific research is the requirement for estimation of the appropriateness of the H_2S dependent treatments for particular NDD for instance AD, PD in addition to HD, as well as individualized medicine strategies need exploration for generation of the tailored treatments dependent on the personal disease profiles as well as patient features. Evaluating the plausible synergistic actions of H_2S dependent treatments with the prevailing therapies or the agents which

are emerging might be resulting in the generation of the novel combination treatments that escalate neuroprotection in addition to modifications of the disease events.Shifting H_2S dependent treatments from the preclinical work to clinical trials would thus envisage well fashioned -translational studies for guaranteeing the safety, effectiveness along with dosages advocated. Neuroimaging strategies might be of value in provision of the understanding in the modes of effects as well as plausible advantages of H_2S dependent treatments. Detection of the ideal therapeutic window in addition to isolation of the dependable biomarkers regarding monitoring treatment reactions are further key steps regarding advancements of H_2S dependent treatments for NDD. Highlighting research in these region swould thus open door for different avenues with regards to novel in addition to targeted treatments bridging the gap of efficacious treatments for such inimical disorders.

Conclusions

Epigenetic controlling has been observed to be a crucial estimator in the pathogenesis along with the propagation of the NDD. The crosstalk amongst this H_2S in addition to variable epigenetic modes for instance DNA methylation, histone modifications along with noncoding RNAs pointing that H_2S might be possessing the capacity of impacting gene expression as well as cellular working germane to neurodegenerative diseases. Achieving insight with regards to appropriate epigenetic modes is necessary for the generation of the targeted in addition to efficacious therapeutic approaches. Moreover evaluation of the long term safety, as well as effectiveness of H_2S dependent treatments would thus be key with regards to clinical translation.

Isolation of the ideal strategies, targeting disease particular actions along with the generation of the individualized medicine strategies would thus guarantee efficacious H_2S dependent treatments. Further research over novel combination treatments in addition to production of the germane biomarkers regarding monitoring treatment reactions are further key steps regarding advancements of H_2S dependent treatments for NDD.In total evaluation of the part of the H_2S in epigenetic controlling as well as NDD portrays an advantageous treatment panorama for NDD, yielding hope to both patients in addition to their families. Furthermore Muntenau C, et al. [95] have extrapolated this for exploiting the part of this knowledge for the treatment of Alzheimer's disease see Figure 2 in addition to disease correlated with OS [92].

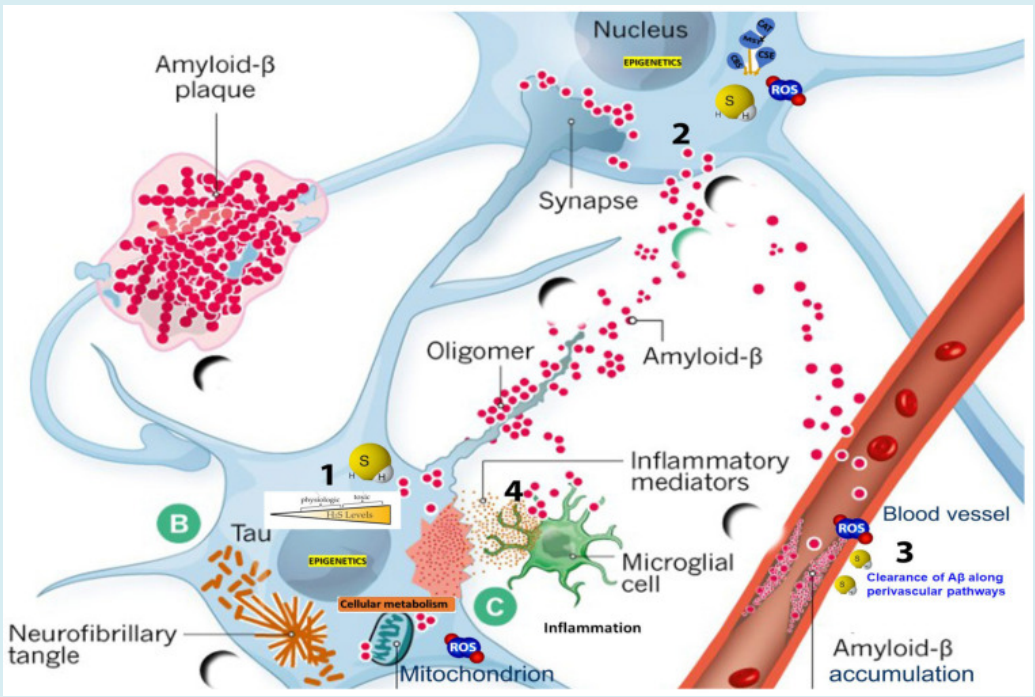

Figure 2: Muntenau C, et al. [95] multifaceted roles of H_2S in Alzheimer's disease. 1: Biphasic, concentration-dependent effects of H_2S, emphasizing its dual role as a toxicant at high concentrations and a cellular signaling molecule at low concentrations; 2: H_2S's involvement in redox homeostasis, emphasizing its protective role in mitochondrial function and regulation of oxidative stress; 3: Putative role of H_2S in promoting the clearance of amyloid-beta (Aβ) peptides; 4: Involvement of H_2S in modulating inflammatory pathways.

Thereby the different recent etiopathologies inclusive of alterations in the mitochondrial melatonergic pathways as revealed by Anderson G in common autoimmune conditions like type 1 diabetes mellitus (T1DM), Parkinson's disease,overlap in addition toare implicated in the pathophysiology of different cancers Amyotrophic Lateral sclerosis (ALS); giving additional overlapping etiopathologies in different diseases are yielding greater insight in these complex disorders might aid in treatment of these disorders, akin to that thework done by the group of Muntenau C, et al. [95]. have started adding extra role of disturbances in H_2S which is implicated in the controlling of the sustenance of different epigenetic change implicated in the sustenance of synaptic plasticity, avoidance of neuroinflammation, as well as neuronal survival, afflicted in these NDD's as well as a role in diabetes mellitus (DM). These might aid in finding newer therapeutic strategies by utilizing combination treatments targeting all these newer targets.

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