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Review

Epigenetics and Dysfunctional Energy Factors of Neurodegenerative Disease with Therapeutic Potential of H_2O_2 as Neuroprotective Agent

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Abstract: The number of people with neurodegenerative disease continues to increase every year. A new perspective is needed in overcoming this disease. In this review, researchers collected information about epigenetics and energy factors of neurodegenerative disease driven by mitochondria. Mitochondrial epigenetic dysregulation can cause damage to the neuron system. The increase in the amount and interaction of α-synuclein with SAMM50 in the mitochondria is one of the factors causing neurodegenerative disease. As an energy provider in the body, the existence of harmonization in the regulation of mitochondria specifically the mitochondrial outer membrane is important. Hydrogen peroxide (H_2O_2) has neuroprotective abilities to overcome the impairment function of mitochondria in neurodegenerative patients. Based on the computational simulation of this case, it can be used as the basic concept for the development of the role of H_2O_2 in neurodegenerative disease.

Keywords: α-synuclein; energy; H_2O_2; mitochondria; neurodegenerative disease

1. Introduction

Many studies have shown that environmental relationships are able to modulate gene expression so that the concept that genomes are static is no longer relevant [1,2,3]. The concept of epigenetic in relation to neurodegenerative diseases (ND) has to do with the mechanism of maintaining memory without alterations in the DNA sequence by the chromosome phenotype. Where epigenetic is a link between external environmental stimuli and gene expression. Some forms of these mechanisms are PTM (post translational modifications) histones, chromatic remodeling, and covalent modifications of DNA [2,3]. Neurodegenerative disease related to epigenetics certainly cannot be separated from the concept of aging. Aging will naturally always occur to living organisms, the main character of this condition is a progressive decrease in the ability to function from cellular, molecular and physiological levels. The aging process is closely related to the condition of neurodegeneration disease [4,5,6]. ND and its relation to energy supply is also an underline theme of this article. As it is known that neuros in the brain depend on the supply of energy by the mitochondria. Impairment of mitochondria can cause brain dysfunction. One of the main causes is the buildup of α-synuclein in mitochondria [7,8,9]. This condition can be prevented by the use of H_2O_2, which in the brain ischaemia model, provides a neuroprotection effect [10,11,12]. The relationship between neurodegenerative disease, epigenetic, energy supply and the role of H_2O_2 are the main focus of the authors.

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2. Epigenetic in Neurodegenerative disease

In the context of epigenetics, MSA (multiple system atrophy) and PD (Parkinson's disease) can be used as examples. MSA itself is a condition where there is a combination of several disorders including striatonigral degeneration (SND), Shy-Drager syndrome and olivopontocerebellar atrophy (OPCA) [13]. Disturbances in movement in these patients are usually indicated by the loss of large amounts of neuronal cells as well as glial cytoplasmic inclusions (GCI) which have an effect on various structures in the central nervous system [14,15,16]. As is known environmental toxins, especially metals, can result in changes in DNA methylation, RNA interference and histone modification [17]. One example of epigenetics that occurs in the context of MSA is histone acetylation. Histone modification in the form of acetylation is regulated by a pair of enzymes, namely HDACs (histone deacetylases) and HATs (histone acetyltransferase), these two enzymes are responsible for deacetylation and acetylation that occur in nucleosomes with specific sites namely N-termini [18,19,20]. In MSA patients found co-localized HDAC6 in GCIs [21]. In addition to histone acetylation, alterations were also found in microRNA expression in MSA patients. Functional miRNA is known to be closely related to the survival of neurons [22-23]. miR-96 and miR-202 had an upregulation, this condition was followed by a decrease in the Oct1 protein in MSA patients [24,25]. The decrease in oct1 protein levels has an impact on the increased likelihood of neurons experiencing oxidative stress and ending in the process of cerebellar neurodegeneration [25,26]. Parkinson's disease is a movement disorder that can be characterized by the formation of Lewy bodies involving the localization of α-synuclein and the reduction of dopaminergic neurons in the substantia nigra pars compacta [27]. Meanwhile, in PD factor patients, epigenetic dysregulation also occurs which can be seen in Table 1.

Table 1. Studies overview of epigenetic mechanism in PD.

Subject	RNA	Effect	Main Result	Target	Ref
Human, MPP⁺-SH-SY5Y cells	miR-214	↓	Increasing the aggregation of α-synuclein, leads to mitochondrial damage	SNCA	[28]
	miR-34b/c	↓	Increasing the mitochondrial fragmentation and lowering ATP concentration	DJ-1 and Parkin	[29,30]
	miR-376a	↑	Downregulation of PGC-1α and TFAM	PGC-1α	[31]
Human	miR4639-5p	↑	Downregulation of DJ-I expression	DJ-I	[32]
	miR-494	↑	Downregulation of DJ-I expression	DJ-I	[33]
Norad knockout-mice	LncRNA-Norad	↓	Mitochondrial dysfunction and instability in genomic	PUM2	[34]
MPP⁺-SH-SY5Y cells	LncRNA-HOTAIR	↑	Inhibiton of miR-205 that leads to apoptosis and mitochondrial damage	miR-205-5p-LRRK2	[35]
Zebrafish	CDR_{las}	↑	Upregulate of SNCA (Neuronal Damage)	SNCA	[36]
Transgenic C-elegans model of PD	circSNCA	↓	Accumulation of alpha synuclein (Neuronal Damage)	SNCA	[37]
PGC-1α null mice	miR-485	↑	Accumulation of alpha synuclein	PGC-1α	[38]
MPP⁺-SH-SY5Y cells	LncRNA-UCA1	↑	Mitochondrial dysfunction and leads to apoptosis	P13K/Akt signaling patwhays	[39,40]

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3. Mitochondria role in neurodegenerative disease

Mitochondrial function in the body is very important which acts as an energy provider. In the context of neurons require ATP (adenosine triphosphate) through a oxidative phosphorylation process. Dysfunction in the mitochondria can cause impairment in ATP biogenesis. The survival viability of the neurons is in a critical phase in case of dysfunction in the mitochondria. There are various kinds of neurodegenerative diseases that have been studied in relation to mitochondrial function. The oxidative phosphorylation complex is deficient in some diseases related to the nervous system. NADH dehydrogenase (Complex I) in Parkinson's disease (PD) was damaged and found in platelets and substantia nigra patients [41,42].

In addition, related proteins related to PD are also related to mitochondria. These proteins include α-synuclein, PINK1, DJ-1 and parkin [43.44]. Another complex is Complex IV which is cytochrome c oxidase, where there is a decrease in the activity of the complex in people with PD. Meanwhile, ATP synthase (Complex V) in PD patients also experienced a decrease in enzyme activity [43]. Other diseases such as Alzheimer's disease (AD) also show a decrease in the number of Complex I and II in the mitochondria. Meanwhile, Complex IV in AD patients experienced a decrease in activity [44-48]. Some proteins that have a relationship with other mitochondria of AD patients is the amyloid precursor protein (APP). APP is associated with outer proteins and inner membrane mitochondria The APP mutation can cause cell death as well as an increase in mitochondrial fission. Proteins in mitochondrial membranes such as SAMM50, VDAC and TOMM20 can interact directly with α-synuclein (Figure 1). α-synuclein is proven to be one of the causes of a wide variety of neurodegenerative diseases. The accumulation of large amounts of α-synuclein will trigger the oxidation of proteins in the mitochondria as well as an increase in reactive oxidant species (ROS) [49,50].

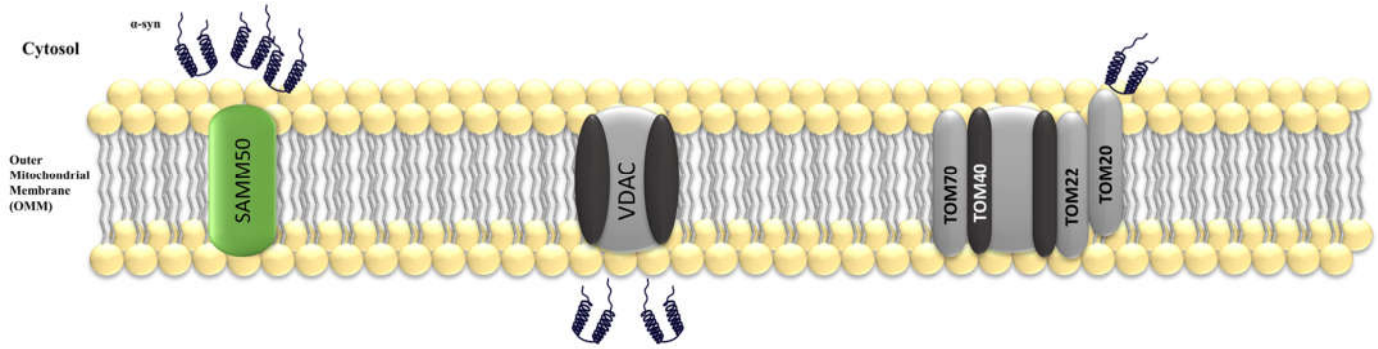

Figure 1. Outer mitochondrial membrane and α-synuclein.

4. Mitochondrial electron transport chain dysfunction in neurodegenerative disease

As stated earlier that the role of mitochondria is very important in the supply of energy to the body. In patients with MSA, mitochondrial dysfunction was found which resulted in a decrease in the number of Coenzyme CoQ10 [51,52]. Coenzyme CoQ10 is very important for its function as an electron carrier and cellular antioxidant. In the mitochondrial electron transport chain (ETC), CoQ10 carries electrons from complex I and II to Complex III [53]. The decrease in the number of Coenzyme CoQ10 is due to damage to CoQ2, where the function of CoQ2 is the encode coenzyme-Q2-polyprenyltransferase involved in the synthesis of coenzyme Q10 [54]. In MSA patients, a decrease in CoQ10 levels was found in CSF (cerebrospinal fluid) and tissues as well as in plasma [55]. Research in Japan [56] showed that there was a decrease of up to 30% in CoQ10 levels in the plasma of MSA patients when compared to control. In addition, in other studies, there was also a decrease in the number of CoQ10 by 40% in 12 MSA patients [57]. A 2019 study published by Nature [58] showed that there was a change in the activity of the ETC component where MSA patients in the cerebellar white matter section of Complex I and

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IV experienced an increase and decrease in Complex II / III. Meanwhile, in PD patients in the occipital white matter section of Complex II / III, there was a decrease and an increase occurred in Complex I. While both MSA and PD patients found that there was no change in the mitochondrial mass.

5. α-Synuclein

The α-synuclein protein (Figure 2) consists of 140 aa (amino acids) with amino acid residues 1-60 constituting the N-terminal region having a positive charge. Amino acid 61-95 is the part involved with the aggregation of α-synuclein referred to as NAC (non-amyloid-beta component). The last part (96-140) of this protein is the C-terminal domain. The NAC domain part of this protein is protected by two other parts which causes the protein not to be easily aggregated [59,60,61]. Mutations caused by environmental conditions in α-synuclein occur due to environmental factors. The six point-mutations are A53E, A53T, E46K, H50Q, A30P and G51D [62-66]. All mutations are located on the N-domain and do not affect the secondary structure changes of α-synuclein [67]. In A30P mutases, α-synuclein is more easily subjected to oligomerization, whereas in A53T and H50Q the probability of protein aggregation increases [68,69]. The increase in the amount of α-synuclein in the mitochondria causes the complex I function to be damaged, whereas if this protein in low quantity then the mitochondrial function can be maintained [70,71,72]. Oligomers of α-synuclein are able to penetrate lipid bilayers as well as intracellular membrane structures [73,74,75]. Inhibition of tubulin polymerization is also one of excess presence impact from α-synuclein in the system [76]. Overexpression of α-synuclein also results in destabilization of microtubules and cytoskeleton cells [76,77].

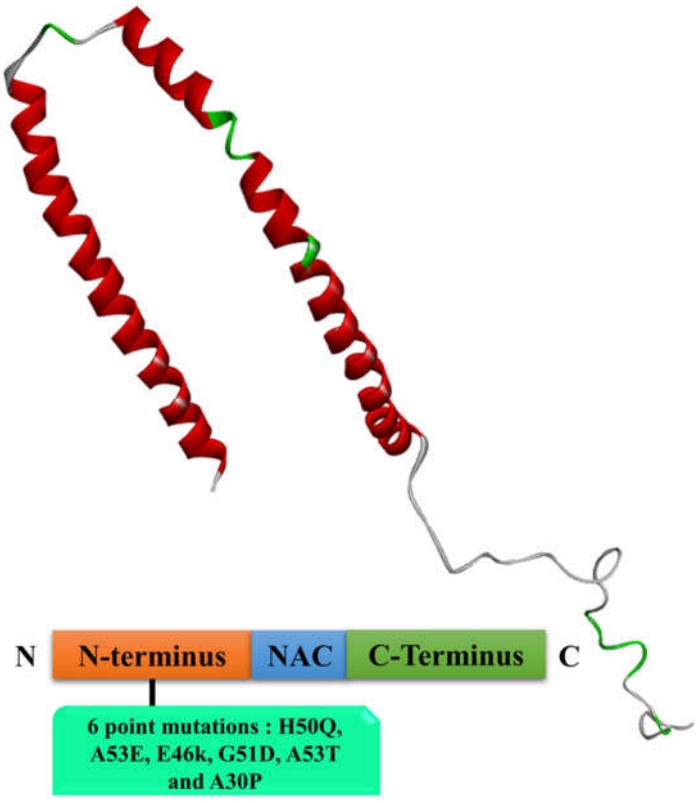

Figure 2. α-synuclein and six point mutations.

6. Energy management in mitochondria and its direct effects on neurodegenerative disease

As it is known that the presence of mitochondria is an important key of the survivability of neurons in the human body. Various neurodegenerative diseases experience

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dysfunctions in energy management associated with mitochondria. The mitochondrial outer membrane (OMM) plays an important role in the translocation of various proteins related to energy metabolism [78,79,80]. Sorting and assembly machinery (SAM) complex is one of the proteins that is in the OMM and has a direct bond with various proteins, one of which is α-synuclein. As previously known, the presence of α-synuclein with large amounts occurs in patients with neurodegenerative diseases such as AD, MSA (multiple system atrophy) and PD (figure 3) [49.50].

In the human body itself there is a mechanism of handling damaged mitochondria. Damaged mitochondria will be degraded by lysosomes through a selective process called mitophagy [81,82,83]. One of the proteins that plays an important role in the mitophagy is GABARAPL1 [84,85,86]. Research by Abudu et al. (2021) showed results that SAMM50 has a very strong interaction with GABARAPL1, so that the function of mitophagy can work properly and maintain harmony of the body's energy system [87]. In the process of mitophagy, mitochondria will release their components such as mtDNA with cardiolipin. These molecules will be accepted by the body system as DAMPs (danger-associated molecular patterns) and will trigger innate immune signals [88].

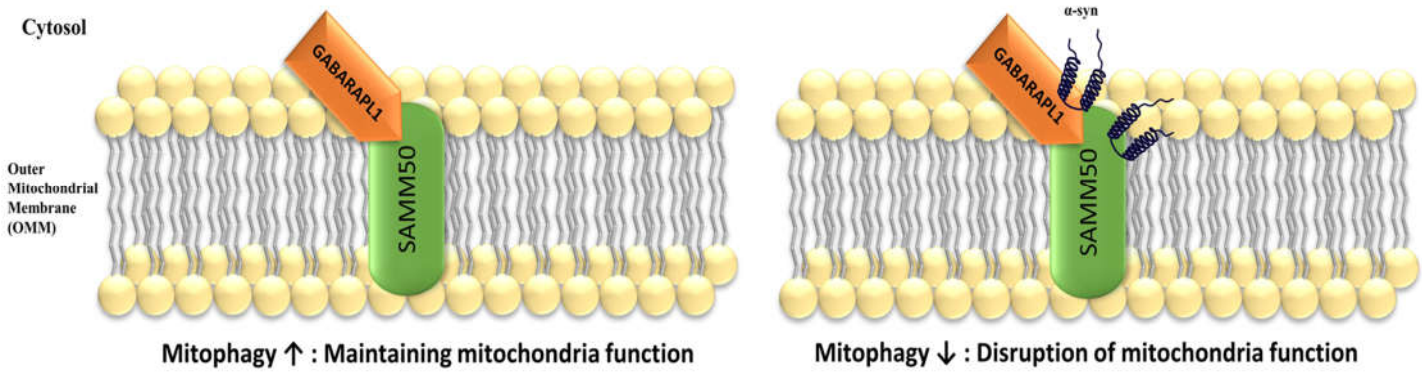

Figure 3. Schematic model of SAMM50, GABARAPL1 and α-synuclein association.

7. Neuroprotection effect of H_2O_2 in neurodegenerative disease

H_2O_2 molecules are often considered toxic molecules that have a negative impact on various levels of life both at the cellular and tissue levels [89,90]. However, many studies have found that the concentration of H_2O_2 affects the function of the molecules in the body. Low concentrations of H_2O_2 are able to provide a wide range of benefits [10,11,12]. Through the help of the enzyme catalase (CAT) this molecule will be broken down into H_2O and ½ O_2. The result of the breakdown, especially O_2, is able to become an alternative supply in the body and reduce the production of reactive oxidant species. Various studies have shown that the H_2O_2 molecule has various positive functions, especially as a regulatory signal in the metabolism [91-99]. It was found that the presence of a small amount of H_2O_2 in the rat brain could be a modulator of plasticity [100-103].

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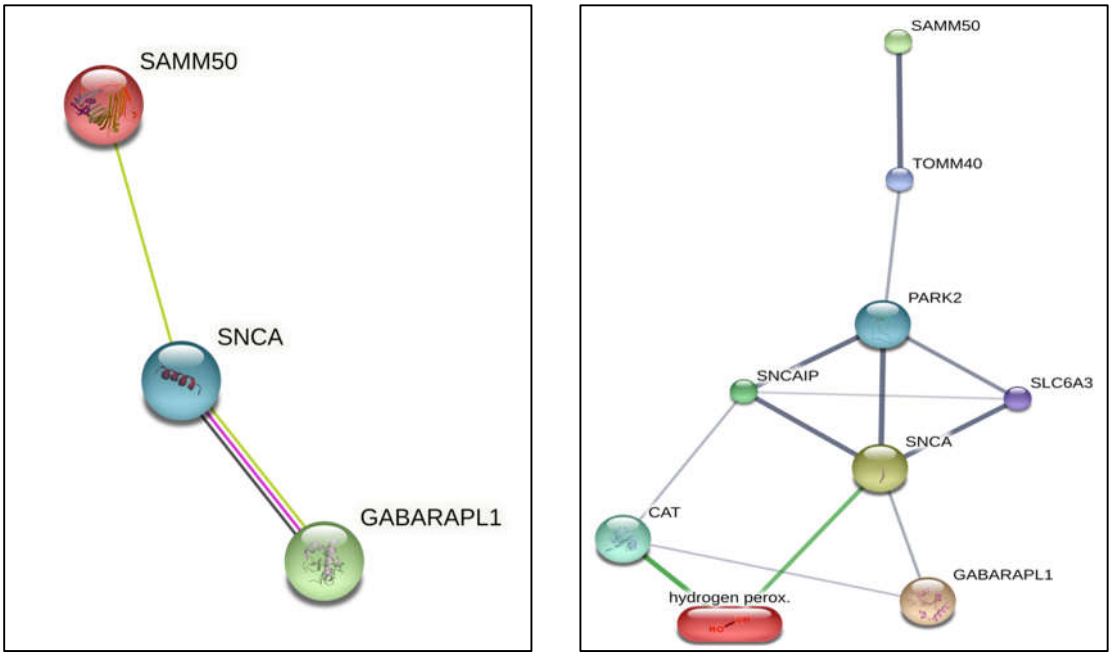

Figure 4. Overview schematic of H_2O_2 addition to GABARAPL1+SAMM50 and α-synuclein.

In addition, it is able to modulate synaptic transmission [104,105,106]. Neuroprotective effect using H_2O_2 found at low concentrations of 10 μM can protect PC12 cell lines from induction of apoptosis, this means that the administration of molecules in low concentrations has a positive impact on mitochondrial functional improvement. In addition, cerebral infarction decreased in H_2O_2 administration by 2 mM [107,108]. Based on the above explanation, the context of α-synuclein abundance in mitochondria, especially SAMM50 protein, will cause impairment of mitochondria which will eventually have implications for neuron damage in ND patients [49,50]. As well as the relationship between GABARAPL1 which is a protein with the role of maintaining mitochondrial function [87], the addition of H_2O_2 molecules in the system will have a neuroprotective impact on the GABARAPL1 and SAMM50 complexes through binding to the α-synuclein protein and the SAMM50 + GABARAPL1 complex (Figure 4).

Data from string (https://string-db.org) and STICH (http://stitch.embl.de) databases show that the SAMM50, α-synuclein (SNCA) and GABARAPL1 proteins have interactions (Figure 5). The interaction score between SAMM50 and α-synuclein was 0.457 while GABARAPL1 with α-synuclein was 0.680. Interaction analysis shows that directly and indirectly H_2O_2 can interact with all proteins (GABARAPL1, α-synuclein or SAMM50).

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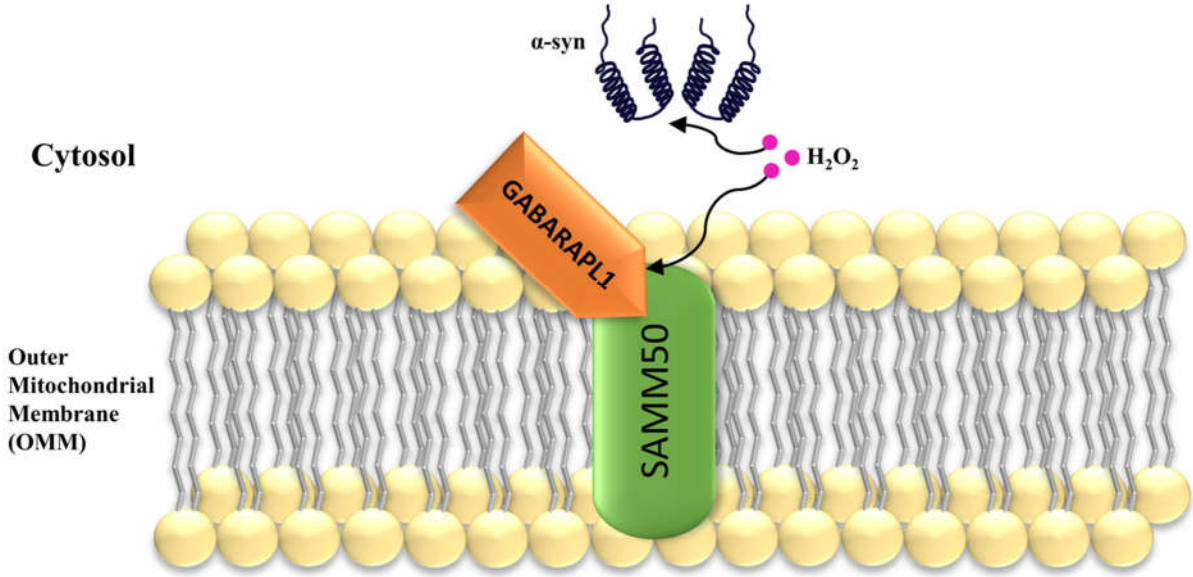

Figure 5. Interaction between molecules H_2O_2 and proteins (α-synuclein, GABARAPL1 and SAMM50).

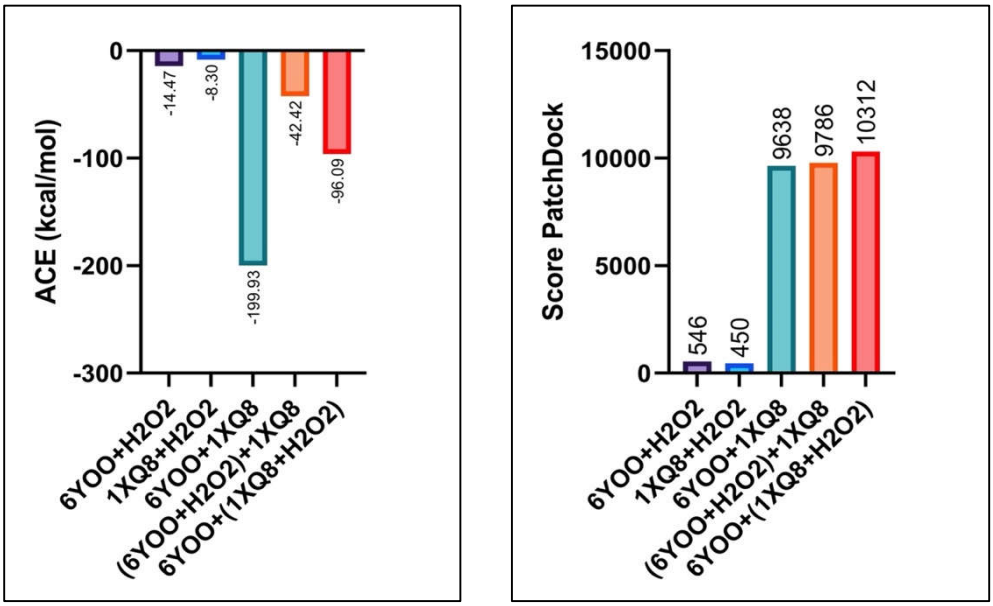

Figure 6. ACE (Atomic Contact Energy) and docking score from PATCHDOCK.

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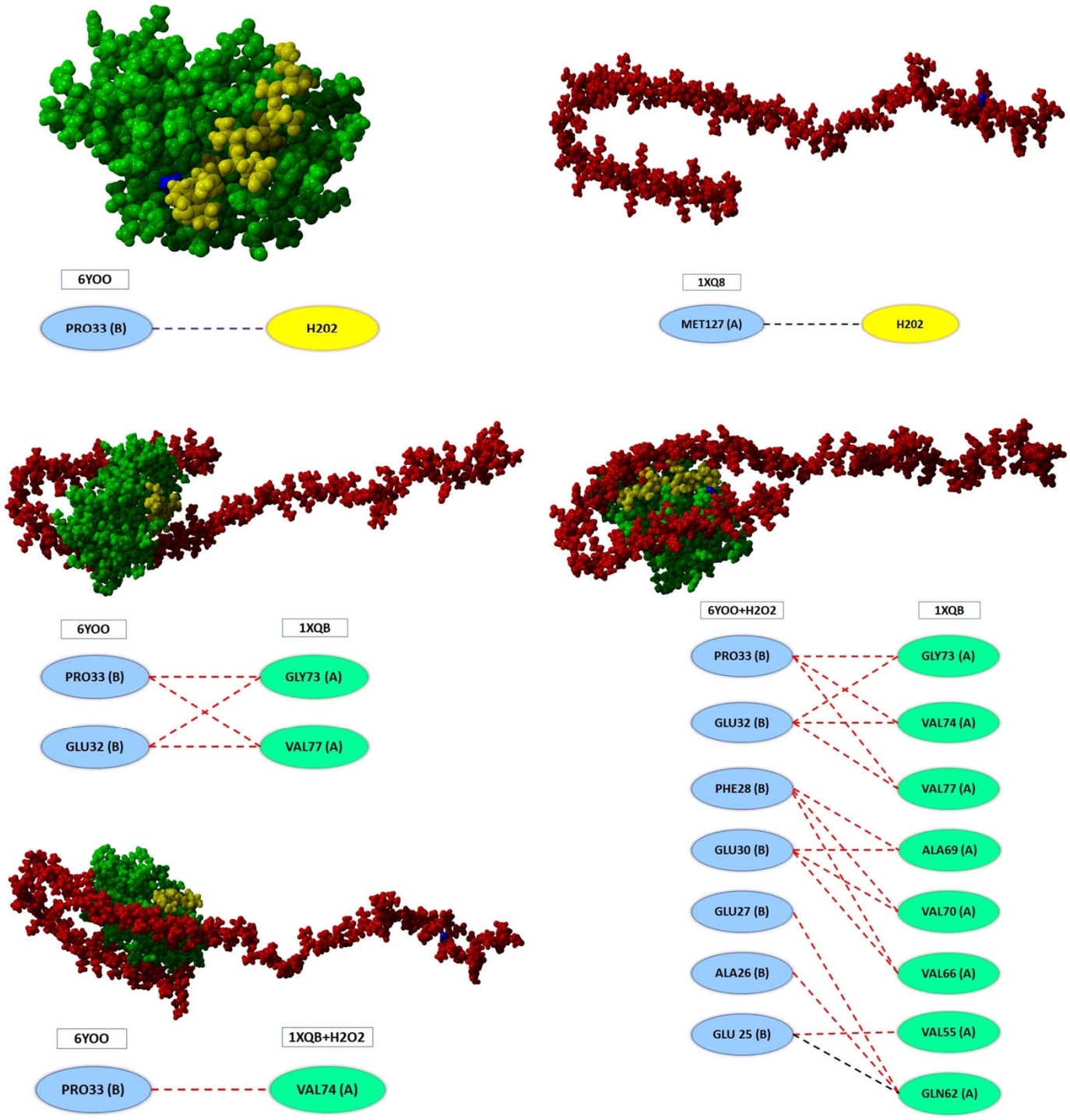

Figure 7. Interaction between 1XQB (α-synuclein protein), 6YOO (GABARAPL1+SAMM50) and H_2O_2. Colours description : 6YOO (Green : GABARAPL1; Yellow : SAMM50; Blue : H_2O_2) , 1XQB (Red : α-synuclein; Blue : H_2O_2) and Arrows (Red lines : Hydrophobic Bond; Black line : Hydrogen Bond).

H_2O_2 can provide neuroprotective effects by enlarging the bond energy required by the α-synuclein protein (1XQ8) to bind to GABARAPL1+SAMM50 (6YOO). When the H_2O_2 molecule binds to 6YOO it requires energy of -14.47 kcal/mol while in 1XQ8 it is -8.30 kcal/mol (Figure 6). Docking analysis [109-112] means that if the hydrogen peroxide

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molecule is in the system, H_2O_2 will more easily bind to the GABARAPL1 + SAMM50 protein complex first and then to α-synuclein.

Then the impact of the binding of such molecules to the protein complex causes a change in the bond energy between the proteins α-synuclein and the GABARAPL1+SAMM50 complex. Before being given hydrogen peroxide molecules the bond between 1XQ8 and 6YOO was -199.93 kcal/mol. Then after being given the H_2O_2 molecule on α-synuclein the energy of interaction with the GABARAPL1+SAMM50 complex becomes -96.09 kcal/mol. While the addition of molecules to the GABARAPL1 + SAMM50 complex has a bond energy of -42.42 kcal/mol. The increase in energy requirements for binding means that H_2O_2 reduces the probability of binding α-synuclein in the mitochondrial complex so that the mitochondrial function as an energy producer for neurons is maintained.

The binding site between protein-protein amino acids may explain the role of H_2O_2 in the 1XQB and 6YOO complexes. In patients with neurodegenerative disease α-synuclein binds to the SAMM50 and GABARAPL1 protein complexes have interactions between the amino acids PRO33(B) and GLU32(B) of GABARAPL1+SAMM50 and GLY73(A) and VAL77(A) in α-synuclein. Whereas after H_2O_2 administration the bonding site has two different effects between its complexes, where in α-synuclein+H_2O_2 when binding with GABARAPL1+ SAMM50 experienced a decrease in the number of bonding sites to two where only PRO33(B) remained the same as native (before H2O2 administration). Whereas in α-synuclein when binding with (GABARAPL1 +SAMM50)+H_2O_2 there is an addition of amino acid bond sites, but the results of energy analysis show that the energy required α-synuclein becomes much higher so that the probability of α-synuclein for binding with GABARAPL1+SAMM50 becomes lower. Exploiting neuroprotective strategies based on H_2O_2 through mitochondria concept is possible for future research [100-108]. It needs to be underlined is that the concept of alpha-synuclein is not the only source of the cause of MSA or PD so the roles of other causes besides alpha-synuclein can occur. So that the research direction on neurodegenerative diseases is expected to be more comprehensive in the future.

8. Conclusions

New perspectives to understand the condition of neurodegenerative disease are needed in order to build a concept in the management of the disease. It has been explained that in ND the role of epigenetics and energy can be used as a basis for thinking. There are many factors involved in ND disease, but new focuses such as improving mitochondrial function as energy suppliers for neurons are very interesting to be studied further in the future. In the present review we summarized the relationship of mitophagy in carrying out mitochondrial functional harmony by GABARAPL1 with the mitochondrial OMM protein, namely SAMM50. This functional can be undermined by the presence as well as the α-synuclein interaction in the system. To overcome this, the use of H_2O_2 can be tried in small concentrations. H_2O_2 is proven to be a paradox in the overall concept of ND, where in large quantities it is able to promote various kinds of damaging pathways while in small concentrations it promotes survival pathways. The use of H_2O_2 function as a neuroprotective agent can be one of the important studies in the future.

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