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Key roles of Arg^5, Tyr^{10} and His residues in Aβ–heme peroxidase: Relevance to Alzheimer's disease

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ABSTRACT

Recent reports show that heme binds to amyloid β-peptide (Aβ) in the brain of Alzheimer's disease (AD) patients and forms Aβ–heme complexes, thus leading a pathological feature of AD. However, the important biological relevance to AD etiology, resulting from human Aβ–heme peroxidase formation, was not well characterized. In this study, we used wild-type and mutated human $Aβ_{1-16}$ peptides and investigated their Aβ–heme peroxidase activities. Our results indicated that both histidine residues (His^{13}, His^{14}) in $Aβ_{1-16}$ and free histidine enhanced the peroxidase activity of heme, hence His residues were essential in peroxidase activity of Aβ–heme complexes. Moreover, Arg^5 was found to be the key residue in making the $Aβ_{1-16}$–heme complex as a peroxidase. Under oxidative and nitrative stress conditions, the $Aβ_{1-16}$–heme complexes caused oxidation and nitration of the Aβ Tyr^{10} residue through promoting peroxidase-like reactions. Therefore, these residues (Arg^5, Tyr^{10} and His) were pivotal in human Aβ–heme peroxidase activity. However, three of these residues (Arg^5, Tyr^{10} and His^{13}) identified in this study are all absent in rodents, where rodent Aβ–heme complex lacks peroxidase activity and it does not show AD, implicating the novel significance of these residues as well as human Aβ–heme peroxidase in the pathology of AD.

1. Introduction

Alzheimer's disease (AD) is one of the most common progressive neurodegenerative disorders in the elderly. Many studies have demonstrated that excess amyloid β-peptides (Aβ) in the brain are believed to be the culprits in the neurodegeneration of AD [1–3]. The aggregation of Aβ peptides and generation of reactive oxygen species (ROS) are the two markers of AD and can be responsible for the early oxidative damage observed in AD [3,4]. The role of metal ions (e.g., Cu^{2+}, Fe^{3+}, and Zn^{2+}) in modulating the Aβ aggregation and in generating ROS is being actively investigated due to the fact that brains of AD patients contain abnormally higher levels of metal ions [3,5–7].

Heme, which is a ferroprotoporphyrin IX complex, is essential to the function of a number of proteins. Recent studies show that heme binds to Aβ to form an Aβ–heme complex, which can stabilize the structure of Aβ and inhibit Aβ aggregation [8–11]. However, depletion of biologically required heme by Aβ binding can result in symptoms such as increases in heme synthesis and iron uptake, abnormal iron homeostasis, dysfunction in mitochondrial complex IV, and oxidative stress, etc [8]. On the other hand, the Aβ–heme complex also exhibits increased peroxidase activity with respect to free heme, and can catalyze the oxidation of specific neurotransmitters (such as 3,4-dihydroxyphenylalanine, serotonin) by H_2O_2 [8,9]. This peroxidase activity could be a probable reason for the oxidative damage and abnormal neurotransmission observed in AD patients. The above symptoms are the characteristic pathological features of AD, and thus the formation of Aβ–heme complex opens up a new dimension in AD pathologic research.

Atamna et al. compared heme-binding between human Aβ and rodent Aβ, and found that human Aβ, unlike rodent (i.e., mouse, rat, etc.) Aβ, tightly bound to heme and formed a peroxidase-like complex. Although both human Aβ and rodent Aβ could form aggregates equally, rodents lack AD-like neuropathology [12]. These findings suggest that formation of Aβ–heme peroxidase contributes to human Aβ's neurotoxicity and the increased human susceptibility to AD. The amino acid sequence of rodent Aβ is identical to that of human Aβ except for three amino acids (Arg^5Gly^5, $Tyr^{10}Phe^{10}$, $His^{13}Arg^{13}$) within the hydrophilic region (Fig. 1A), which

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implies possible important roles of the three residues of human Aβ in AD pathology [12]. Furthermore, these amino acids Arg, Tyr, and His are found to participate in heme-binding in heme-proteins and peroxidases [12–15], which drive us to propose that Aβ–heme peroxidase is a key molecular link between these residues present in human Aβ and the increased human susceptibility to AD. Recent results showed that Arg^5 residue was required for Aβ–heme peroxidase activity and His^{13} and His^{14} residues were the heme-binding ligands [16,17].

It is now well established that heme binds to Aβ peptides and the adducts of Aβ–heme complex show higher peroxidase activity than free heme, but the important biological relevance to AD etiology, resulting from human Aβ–heme peroxidase formation, have not been well characterized. In this study, we used wild-type and mutated human $Aβ_{1-16}$ peptides and investigated their Aβ–heme peroxidase activities, and found that Arg^5 and His residues (His^{13}, His^{14}) were critical for human Aβ–heme peroxidase activity. In the presence of oxidative stress (H_2O_2), $Aβ_{1-16}$–heme complex produced dimerization of the peptide through dityrosine cross-linking, and in addition Aβ underwent endogenous nitration at Tyr^{10} when nitrite ($NaNO_2$) was also present. This result was important for the potential pathogenic role of Tyr^{10} in AD, because both dityrosine cross-linking and Tyr^{10} nitration critically accelerated Aβ aggregation and plaque formation [5,14,15], thus implying that the formation of Aβ–heme peroxidase complex under oxidative stress conditions could be a promoting factor for the Aβ aggregation process. Hence, three of these residues (Arg^5, Tyr^{10} and His^{13}) absent in rodent Aβ and formation of human Aβ–heme peroxidase can play a vital role in AD pathology, while rodent Aβ–heme complex lacks peroxidase activity and it does not show AD.

2. Materials and methods

2.1. Materials

L-Histidine (His), L-arginine, ferriprotoporphyrin IX chloride (hemin, which is referred to as "heme" here), and 2,2′-Azinobis (3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt (ABTS) and rabbit polyclonal antibody against 3-nitrotyrosine were purchased from Sigma. Soluble Aβ peptides ($Aβ_{1-16}$, $Aβ_{17-40}$, and $Aβ_{1-40}$) and the mutated peptides were synthesized by GL Biochem (Shanghai, China) with >95% purity. The $Aβ_{1-16}$ mutants used were Arg^5Asn (R5 N), His^{13}Ala (H13A), His^{14}Ala (H14A), and double mutant His^{13}Gly, His^{14}Gly (H13G-14G).

2.2. Binding of Aβ with heme

Aβ peptides were dissolved in 16% (v/v) CH_3CN/water, while heme solution was prepared in dimethyl sulfoxide [11]. The stock of heme and Aβ was diluted in 100 mM phosphate-buffered saline (PBS, pH 7.0). Aβ–heme complexes were prepared by incubating 1 equiv of both heme and Aβ solutions at room temperature (~25 °C) for 30 min. Then, the complexes were used for peroxidase activity determination.

2.3. Peroxidase activity measurement

ABTS was used as the substrate to measure the peroxidase activity of heme [11,15]. The assay mixture (in PBS, pH 7.0) contained 5 μM heme, 1 mM ABTS, 0.5 mM H_2O_2, and in the presence or absence of Aβ (or free histidine). The peroxidase activity was measured by monitoring the increase in absorbance at 734 nm. The values were the absorptions subtracted by that at 0 min. The kinetic constants (k_{obs}) were obtained from the initial rates of the reactions and calculated from absorbance vs. time [15].

2.4. Dimerization and nitration of Aβ

In the presence or absence of sodium nitrite ($NaNO_2$, 1 mM), the reaction was carried out by adding H_2O_2 (1 mM) to a solution containing heme (20 μM) and $Aβ_{1-16}$ (100 μM) in PBS (pH 7.0). The mixture was incubated for 60 min at 37 °C in the dark and then analyzed for dimerization and nitration of $Aβ_{1-16}$. Significant protein modifications were observed in short time incubation when high concentrations of heme-H_2O_2-NO_2^- were used in many in vitro experiments [10,11,15]. These high concentrations were, therefore, chosen in our studies to conveniently compare the different effects of Aβ–heme complexes.

Dityrosine (3,3′-dityrosine), an oxidation product of tyrosine produced by reaction between tyrosyl radicals, is a highly stable marker of tyrosyl radical activity and an intensely fluorescent compound. The formation of dityrosine (Aβ–Aβ dimeric peptide) was analyzed by measuring fluorescence spectra [5]. Dityrosine fluorescence was excited at 320 nm and monitored at 350–500 nm. Fluorescence intensity was measured at 410 nm. The spectra were recorded with a fluorescence spectrophotometer PerkinElmer-LS55.

Dot blotting was usually performed in detecting protein tyrosine nitration [14]. A rabbit polyclonal antibody against 3-nitrotyrosine was used for detection of the nitrated Aβ peptide in this study.

2.5. Statistical analysis

All of the experiments were performed at least three times. The results were reported as the means ± SD of at least triplicate determinations. One-way ANOVA was used for statistical analyses, and $p < 0.05$ was considered significant.

3. Results and discussion

3.1. His residues were essential in peroxidase activity of Aβ–heme complexes

It is well-known that heme binds to Aβ peptides in the hydrophilic portion (residues 1–16) and His residues are found to be the possible binding ligands [16–18]. Thus, $Aβ_{1-40}$, $Aβ_{1-16}$ and $Aβ_{17-40}$ fragments were used to investigate the possible relationship between histidine-bound complex and peroxidase-like active site. By following the catalytic oxidation of the substrate ABTS by H_2O_2, the peroxidase activities of free heme and Aβ–heme complexes were investigated. Compared with the free heme, both $Aβ_{1-40}$-heme and $Aβ_{1-16}$-heme complexes showed obviously higher and similar peroxidase activities, while $Aβ_{17-40}$-heme complex showed no enhanced peroxidase activity (Fig. 1B). The result further indicated that the hydrophilic N-terminal of Aβ was involved in heme binding [16–18], and played an important role in promoting the peroxidase activity of heme. This peroxidase activity of Aβ–heme complexes (with k_{obs} of 4.2×10^{-3} min^{-1}) was ~3 times faster compared to that of free heme (with k_{obs} of 1.5×10^{-3} min^{-1}), similar to a previous study [16].

Recent studies have shown that His^{13} and His^{14} residues in the N-terminal hydrophilic region of Aβ are the heme-binding ligands, and His^{13} binds to the iron center of heme preferentially when both residues are present [16–18]. Due to the similar active site environments of the heme-bound complexes in $Aβ_{1-40}$ and $Aβ_{1-16}$, $Aβ_{1-16}$ and site-directed mutants of $Aβ_{1-16}$ including single mutants (His^{13}Ala, His^{14}Ala), and double mutant (His^{13}Gly, His^{14}Gly) were thus used to observe the effect of His residues on peroxidase activity of Aβ–heme complexes. As shown in Fig. 1C, the double mutant (His^{13}Gly, His^{14}Gly) showed no enhanced

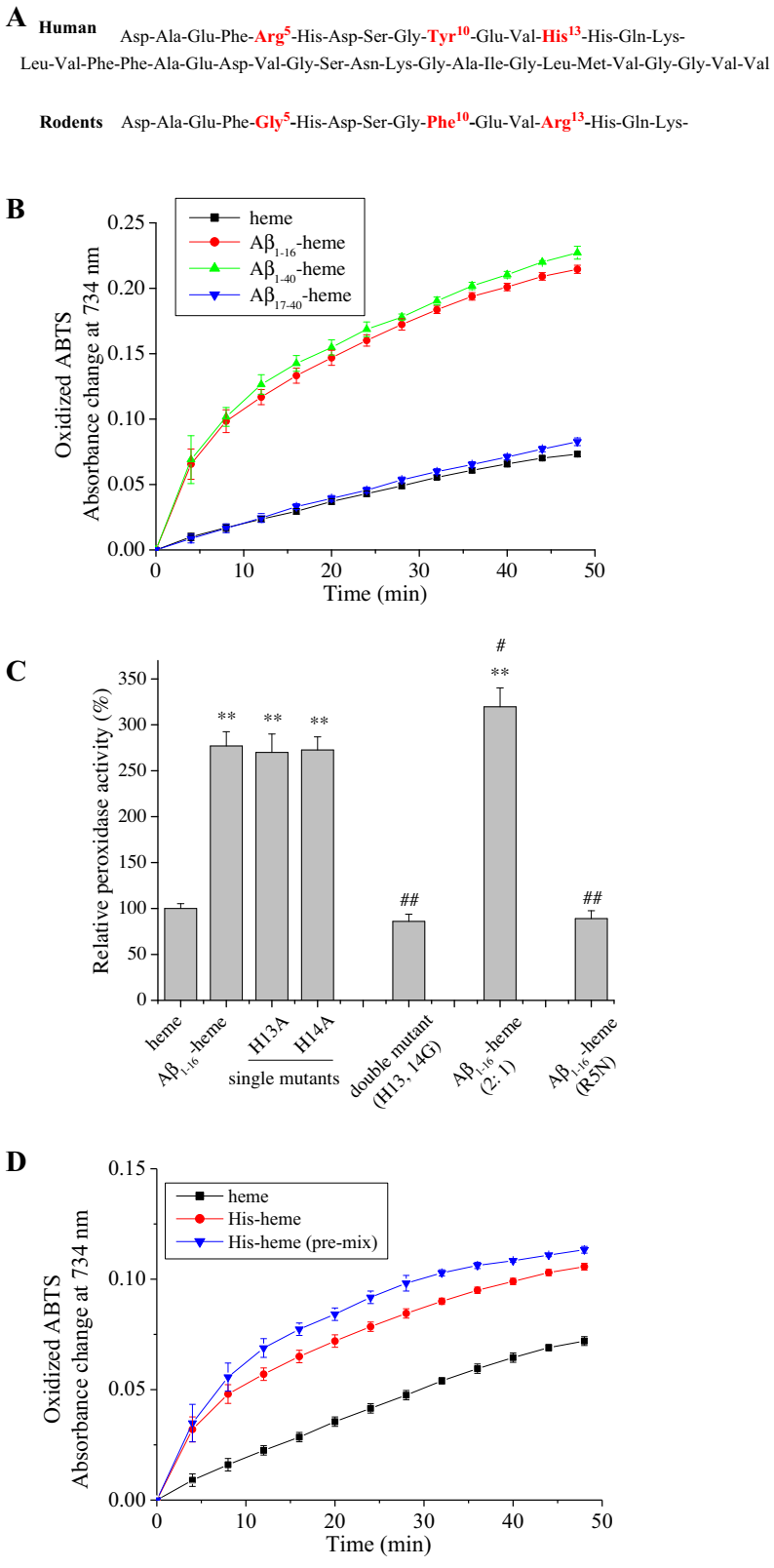

Fig. 1. (A) Amino acid sequence of human $A\beta_{1-40}$ and rodent $A\beta_{1-16}$. (B) Effects of different Aβ peptides on the peroxidase activity of heme. The peroxidase activities were evaluated by relative ABTS oxidation, monitoring the increase of the 734 nm absorbance intensity. ABTS (1 mM) was treated with heme (5 μM)-H_2O_2 (0.5 mM) (control), and in the presence of different Aβ peptides ($A\beta_{1-16}$, $A\beta_{17-40}$, $A\beta_{1-40}$) binding. (C) Effect of His and Arg residues in $A\beta_{1-16}$ on heme peroxidase activity. The reaction mixtures (in 0.1 M PBS) containing ABTS (1 mM), H_2O_2 (0.5 mM), heme (5 μM, control group), and in the presence of different $A\beta_{1-16}$ peptides (single, double His mutants, and Arg^5 mutant, 5 μM, $A\beta_{1-16}$:heme = 1:1) binding with different concentrations ($A\beta_{1-16}$:heme = 1:1 or 2:1) were incubated at 37 °C for 2 h. The corresponding analysis for relative peroxidative activity was obtained. (D) Effects of free His on the peroxidase activity of heme. ABTS (1 mM) was treated with heme (5 μM)-H_2O_2 (0.5 mM) (control), and in the presence or absence of His. His-heme group represented the control group plus free His (50 μM), His-heme (premixed) group represented the control group plus pre-reacted His-heme (50 μM) (t = 10 min). The values were the absorption subtracted by that at 0 min and presented as means ± SD of three independent experiments. The respective control values were set to 100%, to which the other values were compared. $^{**}p < 0.01$ compared to control group, $^{\#\#}p < 0.01$, $^{\#}p < 0.05$ compared to $A\beta_{1-16}$–heme group.

peroxidase activity compared to free heme. The result demonstrated that histidine residues (His^{13}, His^{14}) in $A\beta_{1-16}$ were essential in peroxidase activity of $A\beta_{1-16}$-heme complex and the formation of histidine-bound Aβ complex had high peroxidase-like active site, which was consistent with the fact that $A\beta_{1-16}$ with the double mutant did not bind heme [16,17]. The single mutants of $A\beta_{1-16}$ (His^{13}Ala and His^{14}Ala) showed peroxidase activity comparable to that of the wild-type $A\beta_{1-16}$ peptide (Fig. 1C). This implied that the changing of the coordinating histidine residues did not significantly affect the peroxidase activity of Aβ–heme complex, although the active sites were not identical for His^{13}- and His^{14}-bound heme complexes. In addition, the peroxidase activity of $A\beta_{1-16}$-heme complexes increased slightly with an increase in the ratio of $A\beta_{1-16}$ to heme (from 1:1 to 2:1). This data suggested that the coordinated histidine residues in $A\beta_{1-16}$-heme complexes did not inhibit the interaction between the iron(III) center and H_2O_2, possibly due to the lability of the iron axial ligands [15].

Furthermore, free His was selected to investigate the important role of His on heme peroxidative activity. Similar to the peroxidase activity of Aβ–heme complexes (Fig. 1C), the presence of free His enhanced catalytic activity of heme (Fig. 1D). Moreover, the premix of His and heme for 10 min before adding to the reaction mixture showed more significant enhancement on heme peroxidase activity than when adding His and heme to the reaction mixture one by one (Fig. 1D), further demonstrating that the binding of free His could promote heme catalytic activity. The similar enhancement on heme peroxidase activity was observed for the addition of free imidazole (data not shown). Taken together, these results herein indicated that both histidine residues (His^{13}, His^{14}) in $A\beta_{1-16}$ and free histidine were essential for the higher catalytic activity of heme, implying that the Aβ peptide bound to heme through histidine ligands and subsequently enhanced the peroxidase activity of heme.

3.2. Arginine residue was responsible for the peroxidase activity of Aβ–heme complexes

It is generally accepted that an acidic arginine residue exists in the distal side of heme and can serve as the proton source required for peroxidase activity [13,16,17]. As expected, $A\beta_{1-16}(Arg^5Asn)$-heme complex showed no enhanced activity compared to free heme (Fig. 1C). This clearly demonstrated that Arg^5 was important in making $A\beta_{1-16}$-heme complex as a peroxidase. However, no increase in peroxidase activity occurred upon adding free arginine to heme, His-heme complex or $A\beta_{1-16}$-heme complex (Fig. 2). This result indicated that the catalytic role of Arg in peroxidase activity was merely present in the Aβ–heme complex and related to the intact structure of Aβ–heme. In catalytic cycle of Aβ–heme complex, the Arg^5 residue present in Aβ could act as an acid catalyst to promote the cleavage of the peroxide O—O bond, hence making the Aβ–heme complex function as a peroxidase [16,17]. It is important to note that rodent Aβ, which lacks this Arg^5 residue (Fig. 1A), shows no significant enhancement in peroxidase activity relative to free heme [12], similar to $A\beta_{1-16}(Arg^5Asn)$ peptides (Fig. 1C). The result was also consistent with the fact that Arg^5 was the key distal residue required for the Aβ-heme complex to function as a peroxidase.

3.3. Dimerization and nitration of $A\beta_{1-16}$ under oxidative and nitrative stress

Given that the peroxidase activity of Aβ–heme complexes toward external substrates was widely observed, we then investigated whether this peroxidase reactivity could be important when addressed on the endogenous peptide. The characteristic fluorescence spectra of dityrosine at 410 nm were assessed for tyrosine oxidative modification in Aβ [5]. Upon reaction of $A\beta_{1-16}$–heme with H_2O_2, analysis of the peptide showed an increase in the characteristic fluorescence for tyrosine cross-links (Fig. 3A). The dityrosine-contained peptide was only observed in the presence of both

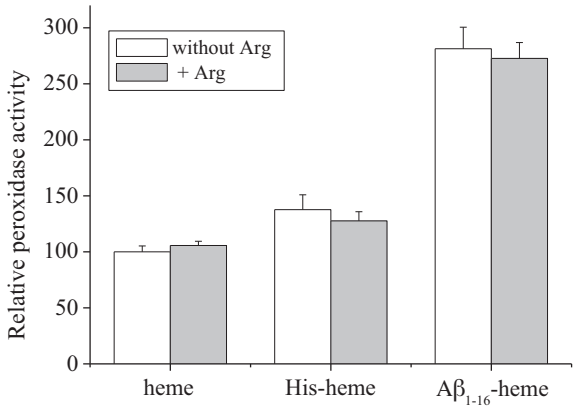

Fig. 2. Potential effect of free arginine on Aβ–heme peroxidase activity. The reaction mixtures (in 0.1 M PBS) containing ABTS (1 mM), H_2O_2 (0.5 mM), heme (5 μM, control group, or His-heme (50 μM), $A\beta_{1-16}$–heme (5 μM)), and in the presence or absence of free L-arginine (50 μM) were incubated at 37 °C for 2 h. The values were the absorption subtracted by that at 0 min and presented as means ± SD of three independent experiments. The respective control values were set to 100%, to which the other values were compared.

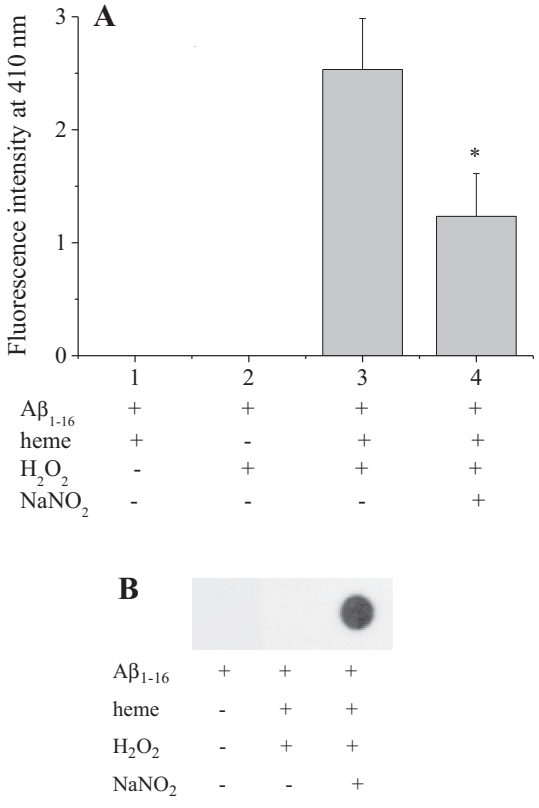

Fig. 3. Dimerization and nitration of $A\beta_{1-16}$ under oxidative and nitrative stress. The mixture containing heme (20 μM), $A\beta_{1-16}$ (100 μM), H_2O_2 (1 mM), and in the presence or absence of $NaNO_2$ (1 mM), was incubated in PBS (pH 7.0) for 60 min. (A) The fluorescence intensity of dityrosine formation was measured at 410 nm. The values presented as means ± SD of three independent experiments. $^*p < 0.05$ compared to control group (heme-H_2O_2 treated, group 3). (B) Tyrosine nitration was determined by dot blotting using 3-nitrotyrosine antibody.

heme and H_2O_2. The formation of dityrosine was also confirmed by the dot blot of the peptide by using dityrosine antibody (data not shown). The presence of Tyr^{10} in Aβ enabled us to infer the formation of 3,3′-dityrosine cross-link between the two $Aβ_{1-16}$ chains. In heme peroxidase cycle, ferryl intermediates can oxidize tyrosine residues in Aβ to highly reactive tyrosyl radical, which can rapidly react with another tyrosyl radical and recombine to dityrosine-contained dimeric peptide (Fig. 4). The similar types of cross-link were previously observed by peroxynitrite-induced dityrosine cross-linked Aβ [14], and the copper(II)–H_2O_2-mediated oxidation of Aβ [5]. Aβ–Aβ cross-linking via the tyrosine residues increased the structural strength of Aβ, and subsequently made the peptide highly resistant to proteolysis and promoted its oligomerization [5,15].

The reactivity of $Aβ_{1-16}$-heme complex towards H_2O_2 was further investigated in the presence of $NaNO_2$, which typically simulated the oxidative and nitrative stress. Fluorescence spectra analysis at 410 nm showed a decrease in the amount of dityrosine-contained peptide (Fig. 3A). Moreover, heme-H_2O_2-$NaNO_2$ system was a classic tyrosine nitrating agent [19,20], indicating that Aβ would undergo tyrosine nitration. This was confirmed by the dot blot of the peptide by using 3-nitrotyrosine antibody, and showed the formation of nitrated tyrosine (Fig. 3B). In the absence of $NaNO_2$, Tyr^{10} nitration was not observed. In heme peroxidase pathways, the ferryl intermediates can oxidize $NaNO_2$ and tyrosine residues in Aβ to the concomitant formation of nitrogen dioxide (**.**NO_2) and tyrosyl radicals respectively, which combine to form 3-nitrotyrosine (Fig. 4) [21]. The formation of 3-nitrotyrosine competes with the dimerization of tyrosyl radicals to 3,3′-dityrosine. Thus, the presence of $NaNO_2$ showed an inhibitive effect in Aβ–heme-H_2O_2-induced dityrosine-contained peptide formation (Fig. 3A). A similar tyrosine nitration was observed by peroxynitrite-mediated oxidation of Tyr^{10} in Aβ [14]. Nitration of Aβ Tyr^{10} accelerated its aggregation and plaque formation, and was detected in the core of Aβ plaques of AD brains [14]. Therefore, the endogenous nitration of Aβ by $Aβ_{1-16}$-heme complex in the presence of H_2O_2 and $NaNO_2$, are likely more deleterious than, the exogenous nitration of external proteins (such as glyceraldehyde-3-phosphate dehydrogenase and enolase) by Aβ–heme/H_2O_2/$NaNO_2$ which have been recently reported [19,20]. Similarly, the $Aβ_{1-40}$–heme complex also caused oxidation and nitration of the Aβ Tyr^{10} residue through endogenous peroxidative (H_2O_2) and nitrative (H_2O_2/NO_2^-) activities (data not shown).

Furthermore, evidence suggests that tyrosine is a redox-active center in electron transfer between the bulk phase and heme [22]. A recent study indicates that Tyr^{10} in Aβ provides an electron during the Cu^+ or heme(Fe^{2+}) bound Aβ-mediated $2e^-$ reduction of O_2 to H_2O_2 [6,7]. However, our study showed that the endogenous reactivity of Aβ–heme peroxidase on the Tyr^{10} residue led to the formation of dityrosine cross-linking-contained dimeric peptide, while Tyr^{10} was competitively nitrated when nitrite was also present (Fig. 4). Both modifications strongly enhanced the aggregation of Aβ peptides [5,14,15], thus the formation of Aβ–heme peroxidase could indeed be a factor contributing to neuroinflammation and Aβ aggregation, different from the classic inhibitive effect of heme on Aβ aggregation through Aβ–heme complex formation [8–11]. These findings shed light on the endogenous peroxidative

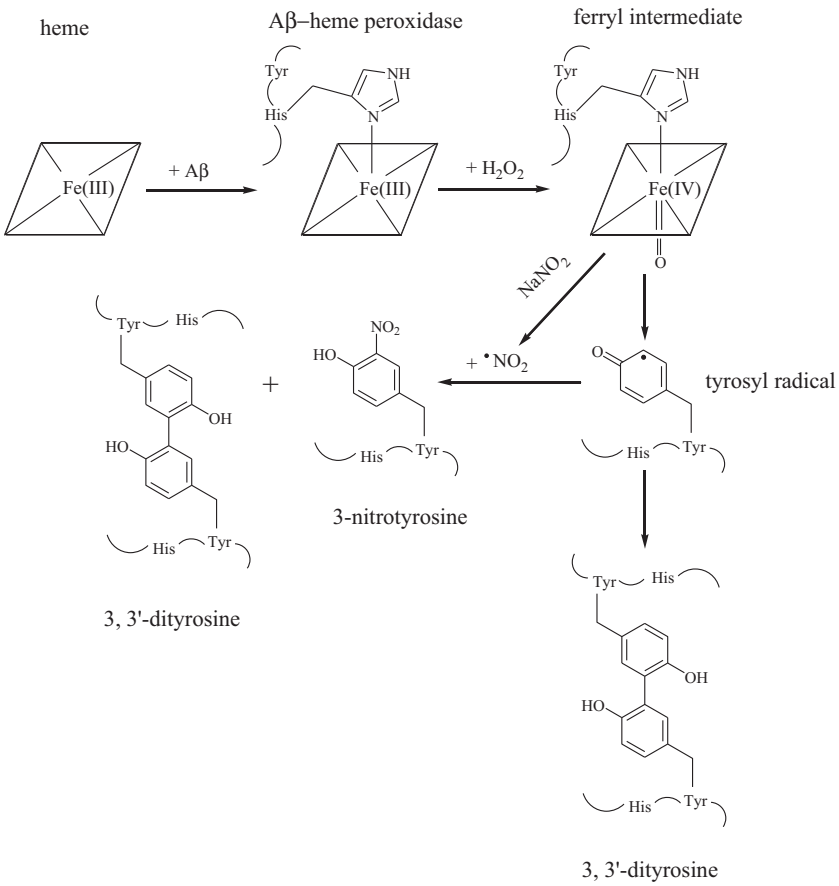

Fig. 4. Aβ–heme peroxidase induced dimerization and nitration of Aβ under oxidative stress. Heme bound to Aβ and formed Aβ–heme peroxidase complexes. Subsequently, the Aβ–heme complexes caused endogenous oxidation and nitration of the Aβ Tyr^{10} residue under oxidative (H_2O_2) and nitrative (H_2O_2/NO_2^-) stress.

and nitrative activities of Aβ–heme peroxidase, which would open new directions for better understanding the important roles of Aβ–heme complex in the pathogenesis of AD.

In summary, we established that His^{13}, His^{14} and Arg^{5} were essential in peroxidase activity of Aβ–heme complexes. Under oxidative (H_2O_2) and nitrative (H_2O_2/NO_2^-) stress conditions, the Aβ–heme complexes caused oxidation and nitration of the Aβ Tyr^{10} residue through promoting peroxidase-like reactions, where both modifications were strongly associated with the aggregation of Aβ peptides [5,14,15]. The fact that the three key residues (Arg^{5}, Tyr^{10} and His^{13}) involved in the active site of human Aβ–heme peroxidase activity are absent in rodent Aβ peptides, is interesting, as rodent Aβ–heme complex lacks peroxidase activity and these rodents do not show AD. This further stresses the importance of these residues as well as human Aβ–heme peroxidase in the neuropathology of AD.

Conflict of interest

The authors declare no competing financial interest.

Acknowledgments

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