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Focused review

Interaction of amylin species with transition metals and membranes

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ABSTRACT

Islet Amyloid Polypeptide (IAPP), also known as amylin, is a 37-amino-acid peptide hormone that is secreted by pancreatic islet β-cells. Amylin is complementary to insulin in regulating and maintaining blood glucose levels in the human body. The misfolding and aggregation of amylin is primarily associated with type 2 diabetes mellitus, which is classified as an amyloid disease. Recently, the interactions between amylin and specific metal ions, e.g., copper(II), zinc(II), and iron(II), were found to impact its performance and aggregation processes. Therefore, the focus in this review will be on how the chemistry and structural properties of amylin are affected by these interactions. In addition, the impact of amylin and other amyloidogenic peptides interacting with metal ions on the cell membranes is discussed. In particular, recent studies on the interactions of amylin with copper, zinc, iron, nickel, gold, ruthenium, and vanadium are discussed.

1. Introduction

Islet Amyloid Polypeptide (IAPP), i.e., amylin, is a 37-residue polypeptide that is stored as a prohormone within secretory granules inside the β-cells of the pancreas before it is processed to mature hormone and secreted extracellularly [1]. Since it is co-localized and co-secreted with insulin in response to nutrient stimuli, the effects of amylin are complementary to the effects of insulin in regulating and maintaining blood glucose levels. Amylin is also a key component of the protein aggregates accumulating in the islets of Langerhans of patients with type 2 diabetes mellitus (T2DM), and it has been implicated in the disruption of the cellular membrane of β-cells [2] by causing membrane-associated stress due to the uncontrolled influx of ions into the cell [3]. Previous preclinical studies [4,5] suggested that amylin has the ability to bind with high affinity to particular regions of the brain, including the area called Postrema. Therefore, it is considered a neuroendocrine hormone with an important role in regulating the rate of glucose influx into circulation after meals. The native form of amylin is amidated at the C-terminus, and has a Cys2 to Cys7 disulfide bridge (Fig. 1) [6,7].

Recent studies correlated the presence of amylin aggregates and their direct toxicity to β-cells [9]; therefore, subsequent studies investigated the possible causes underlying amylin aggregation [10–12]. Other studies [13–15] have shown that human amylin (hIAPP) has the ability to generate hydrogen peroxide (H2O2) during amyloid fibril formation in vitro. Electron Spin Resonance (ESR) detection was used in combination with the Amplex red assay technique [13] to demonstrate that hIAPP, which is amyloidogenic and toxic, generates H2O2 in vitro [14], whereas rat amylin (rIAPP), which is nontoxic and non-fibrillogenic, does not. Also, it is established fact that rats do not develop T2DM. Thus, oxidative stress due to the presence of Reactive Oxygen Species (ROS) is implicated to participate in the development and progression of T2DM. [15,16] However, it has to be mentioned that other authors have reported that there is some of evidence suggesting that also rIAPP may be harmful to β-cells [17–20]. For instance, rIAPP was found to be able to produce comparable H2O2 concentrations, indicating that amylin aggregation and amylin-induced ROS are unrelated processes. [21] It has to be pointed out that some authors demonstrated that the rIAPP(1–37) peptide and its short derivate rIAPP (17–29) are cytotoxic to cultured RIN-M cells, and the previous treatment with antioxidants can revert this effect [18]. These recent studies suggest that the issue of the possible toxicity of rIAPP needs to be clarified during the future studies.

Work on the potential role of metals in amylin aggregation (Fig. 2) has rapidly increased over the last two decades due to its possible biomedical importance [22–24].

Metals such as zinc (Zn), copper (Cu), and iron (Fe), have been widely associated with T2DM and amylin aggregation (Fig. 2) [22–24]. Amylin and Zn^{2+} play an important role in glycemic regulation. Zn^{2+} ions are stored and packed along with amylin in the granules of the β-cells of the pancreas [25,26]; therefore, these granules contain the highest concentration of zinc ions found in the body, reaching up to ~10–20 mM in the interior of the dense granule core [27–30]. Zinc deficiency is common in T2DM [31]. Aggregation of amylin and

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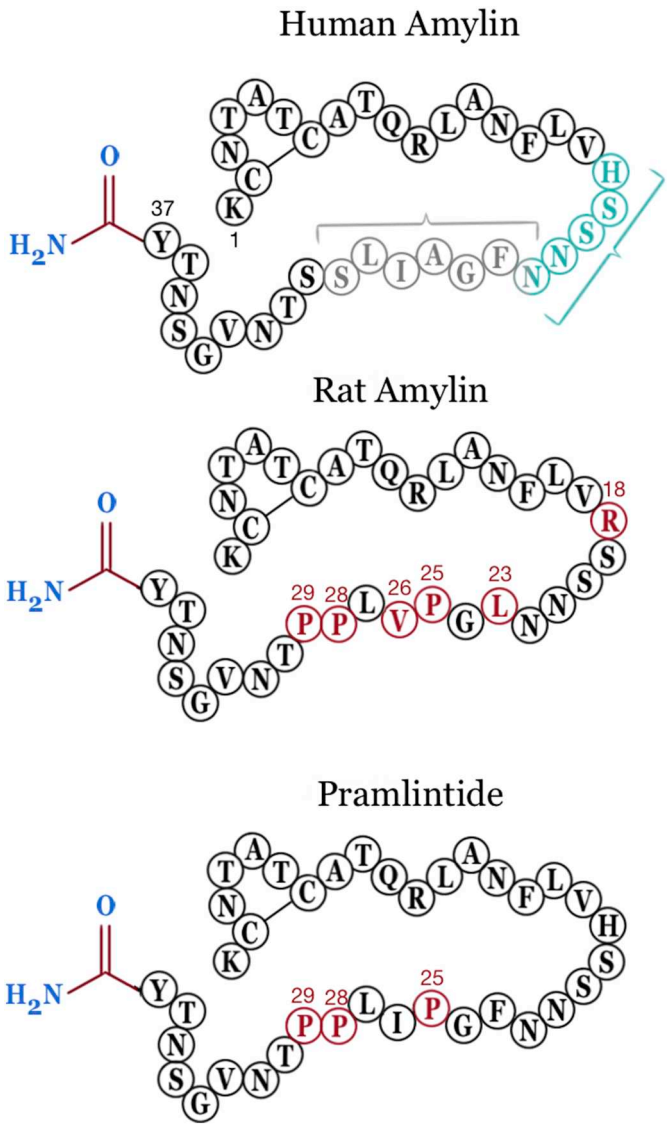

Fig. 1. Comparison of primary structure of analogous amylins.
Primary structures of human amylin, rat amylin, and pramlintide. Differences in residues are emphasized in red. The gray section indicated the amyloidogenic region (22–28) [7]. The cyan section represents the region that exhibits independently high affinity to Cu(II) ions (19–22) [8]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

progression of T2DM occur when the balance of the peptide and zinc(II) ions is disrupted [32,33].

In the case of copper(II) ions, there is controversy about their role in the aggregation of amylin. Some studies mentioned that they can inhibit amylin fibrillation as well as toxicity [24,34], while others indicate that they may contribute to the cell toxicity by forming amylin oligomers, which may contribute to cell death more than the fibrils [21,22].

Iron was shown to enhance amylin β-pleated sheet formation [35]. In form of heme, iron can bind to amylin and form a heme–amylin complex, which leads to the formation of H2O2 via oxidative stress [36,37]. David et al. [38] conducted the only study on nickel so far, and described its coordination mode with the selected shorter fragment (-19SSNN22-) of rat amylin [38].

In addition to metal ions, the pH of solution and the protonation state of histidine 18 (His18) also affect the aggregation, misfolding, and fibrillization of amylin [39]. A recent study of four amylin mutants (His18Arg-IAPP, His18Lys-IAPP, His18Ala-IAPP, and His18Glu-IAPP) revealed that His18 plays a key role in the binding of hIAPP to the cellular membrane [40]. It also explained that (His18) is particularly important for the intra and intermolecular interactions that occur during fibril formation and may involve residue charge, size of the fiber, and hydrophobicity [40,41].

2. Zinc ions

As mentioned above, the secretory granules of β-cells have high concentrations of Zn^{2+} ions [31]. Studies [42–44] have suggested that a missense mutation within the zinc transporter protein ZnT8 of the secretory granule is linked to an increased risk of developing T2DM. Nuclear Magnetic Resonance (NMR) experiments showed that Zn^{2+} ions bind to the His18 residue of the monomeric form of amylin [45]. It was also reported that Zn^{2+} ions bind with the geometry of tetra, penta, and hexahedral coordination sites and coordinate with the amino acid residues within the proteins, with or without the involvement of water molecules [46–48]. However, it was proven that Zn^{2+} ions prefer the tetrahedral coordination mode in which four amino acids or water molecules are coordinated to the Zn^{2+} ion in the complex with proteins [46].

Previously, Ramamoorthy's group reported that the Zn-hIAPP (1–37) complex had a much higher X-ray Absorption Near Edge Structure (XANES) peak than the (1–19) IAPP fragment. This double peak is characteristic of outer-shell scattering, like the one that is seen for imidazoles, implying that the average Zn–imidazole binding is stronger in the Zn–hIAPP (1–37) complex than in the Zn–hIAPP (1–19) complex. Since the hIAPP peptide has only a single histidine, the binding of hIAPP (1–37) to Zn^{2+} may promote higher order aggregates, such as three or four hIAPP peptide molecules per zinc, than the binding of the shorter hIAPP (1–19) fragment [49]. Some experiments that have been done at acidic pH, which causes a partial neutralization of the effect of the change in charge upon Zn^{2+} binding, showed that the observed inhibited aggregation is mainly due to an electrostatic effect that happens at His18 [45].

Ramamoorthy's group also suggested that Zn^{2+} ions promote the formation of amylin fibrils, i.e., cross-β structures of amylin. Further investigation is needed to reveal the effect of the coordination mode of Zn^{2+} ions on the self-assembled cross-β structure of amylin oligomers [27]. According to Ramamoorthy's group, Zn^{2+} ions have different effects on amylin aggregation depending on their concentration and the different stages of the amylin aggregation process itself. At high concentrations (10 mM) and in the early stages of aggregation (40 min), Zn^{2+} ions promote the formation of large Zn^{2+}–amylin aggregates compared with amylin aggregation when Zn^{2+} ions are absent. In the same stages of aggregation (40 min), but at low concentrations (100 μM), Zn^{2+} ions induce the formation of even larger Zn^{2+}–amylin aggregates than those that are formed at high concentrations of Zn^{2+} ions. During the last aggregation stages (in which the amylin fibrils are formed), fiber formation is inhibited at low concentrations of Zn^{2+} and accelerated at higher concentrations (Fig. 2) [45,49]. Although zinc is greatly reducing the total amount of fibers, the overall morphology of the individual amyloid fibers remains almost intact. In conclusion, Zn^{2+} does not significantly promote a breakage of the fiber or greatly alter the lateral attachment of protofilaments to mature amyloid fibers [45].

The biological importance of the zinc ions and their protective effect against diabetes has been underlined by in vivo studies in diabetes induced rats. Zinc acts against diabetes induced peripheral nerve damage by stimulating metallothionein (MT) protein synthesis which has the ability of controlling the oxidative stress. [50] It is also known that zinc supplementation or injection can significantly induce the synthesis of anti-oxidant MT in the pancreatic islets, kidneys, liver and heart of diabetes-induced animals [51–57].

Łoboda et al. [6] used several techniques, including mass spectrometry, potentiometry, NMR and Atomic Force Microscopy (AFM), to

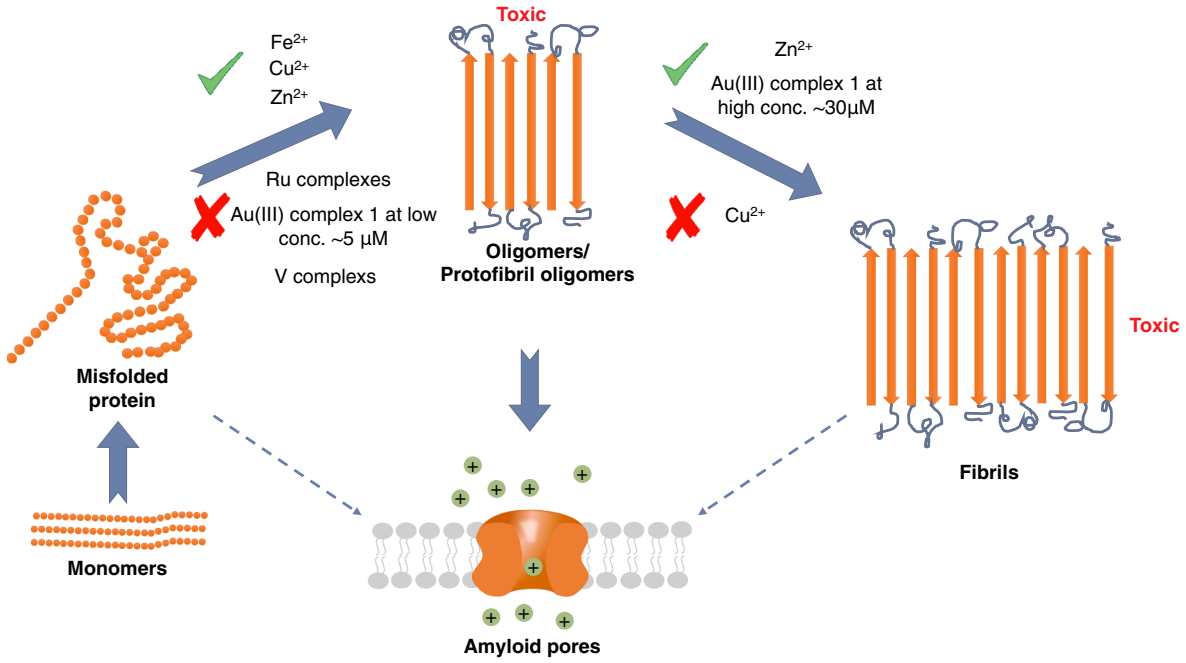

Fig. 2. Schematic representation of peptide/protein oligomerization pathways.
Misfolded proteins can undergo fibril formation, resulting in the creation of oligomeric forms, like protofibrils and mature fibrils. Fe(II), Cu(II), and Zn(II) ions promote the formation of amylin oligomers/protofibrils, while Ru complexes, V complexes, and Au(III) 2 and 3 complexes inhibit it. Complex 1 promotes the formation of amylin oligomers/protofibrils at high concentrations (conc.) (~30 μM); at low concentrations (~5 μM), it inhibits the amylin oligomer formation. Cu(II) ions inhibit amylin fibrillation and reduce toxicity. The role of metal ions in amyloid pore formation still needs to be investigated in detail.

investigate Zn(II)-pramlintide complexes. Pramlintide is a synthetic analogue of human amylin that is an injectable drug used to lower sugar (glucose) levels in the blood [4]. It differs from hIAPP in 3 of 37 amino-acid residues, carrying proline residues at positions 25, 28 and 29 of the peptide chain, respectively, replacing one alanine and two serine residues. Zn(II) ions bind to the His18 imidazole ring of pramlintide and the *N*-terminal amino group of the Lys1 residue, causing loop formation between these residues of the peptide. This complex has much higher stability than the Zn(II)-amylin (1–19) complex, implying that additional stability of the Zn(II)-pramlintide complex comes from interactions with residues (20–37). Region (20–37) of pramlintide also appears to influence the time-delayed fibrillization of the complex. The initial Zn(II)-pramlintide species that is characterized as well-soluble and non-aggregating forms than oligomeric aggregates after a lag-time of 20 h. David et al. [38] performed studies on Zn(II) complexes involving the (16–22) and (19–22) fragments of rIAPP to reveal the role of internal asparagine (21 − 22) residues in anchoring and stabilizing rIAPP. Low-stability complexes were detected that exclusively bind to the amino terminus. The stability constants of the GGHSSNN-NH2 peptide (containing H residue) are much higher than those of SSNA-NH2. The different coordination modes explain this stability difference between the two peptides. Particularly, the only available binding mode for SSNA-NH2 is (NH2,CO), while in the case of GGHSSNN-NH2 the stability of the complexes can be influenced by the imidazole side chain of the histidine residue.

Finally, Luiza et al. [58] focused on the interaction of rat amylin with zinc ions in vitro. The authors stated that the regulation of the rat amylin self-assembly is highly associated with the effects of zinc and pH. To investigate the interaction of zinc with both monomeric and oligomeric rIAPP, they used ion-mobility mass spectrometry (IMS-MS). The binding of zinc ions to rIAPP was confirmed using NMR. Some residues were affected by the zinc ion addition; the most affected in the amide group were Asn3, Thr4, Cys7, Ala8, Val17, and Arg18. The signal of Cys2 became invisible, and the signal of Asn3 significantly decreased. In the aliphatic regions of the 13C-1H Heteronuclear Single Quantum Correlation (HSQC) spectrum, Lys1, Cys7, and Ala13 were the most affected residues. The two Cys residues are the only predicted Zn(II) ions binding sites. In oxidized amylin, however, a disulfide bridge is formed between the Cys residues. As result, one would not expect presence of a particular specific canonical binding site for Zn(II) ions in an oxidized amylin peptide. The current results may suggest transient interactions with positively charged residues, more specifically Arg18 and the *N*-terminal Lys1. Zinc accelerated the process of rIAPP aggregation into amyloid fibrils. The ESI-IMS-MS data showed the binding of zinc to a monomer, a dimer, and a trimer occurring in the low concentration of micromolar range, reaching saturation at about 500 μM. These data provide an indication of the affinity of rat amylin to zinc ions, below the typical concentration of millimolar range that is found in the secretory granules of pancreatic β-cells [58].

All of these findings provide new information about the role of zinc in diabetes, and how it can be beneficial to use pramlintide as an antidiabetic drug, also giving room to think about the formation of the Zn(II)-pramlintide complex, the molecular basis and the role that Zn(II) ions play in the mechanism of fibril formation [6].

3. Copper(II) ions

The interactions between copper(II) ions and amylin were studied by different techniques. A study by Li et al. [8] using Mass Spectrometry (MS) showed that copper(II) disrupts amylin fibril formation by inhibiting the arrangement of amylin dimers. This may involve the creation of a complex from a copper(II) ion and the extended β-hairpin of amylin [8]. Ion Mobility Separation (IMS) was used to evaluate the influence of Cu^{2+} ions on the hIAPP conformation in solution and to detect the Cu^{2+} ion binding sites. These results showed a preferential association between the β-hairpin fragment of the amylin monomer and the Cu^{2+} ion. Moreover, the Cu^{2+} ion bound strongly to the –18HSSNN22– fragment of hIAPP. Amylin dimers were observed in the absence of Cu^{2+} ions, while no dimers were observed in the presence of Cu^{2+} in the solution. The authors concluded that Cu^{2+} ions disrupt the

association pathway leading to the formation of amylin fibrils rich in β-sheet motifs, most likely due to the preferential binding of Cu^{2+} ions to the β-hairpin conformer. Riba et al. [59] found that there are two binding sites for copper ions in full-length hIAPP. One site, alanine 25, is known for its importance for the ability of amylin to misfold. The other binding site is most likely positioned between the 32 and 37 residues, near the C-terminus of the peptide.

Other studies [60,61] used the standard Thioflavin-T (ThT) aggregation assay and Amplex-UltraRed H2O2 detection assays to test the effect of Cu^{2+} on the hIAPP aggregation process, and the resulting formation of aggregates. They proved that the presence of Cu^{2+} increased the activation energy of the reaction, thereby prolonging the lag phase and slowing down the rate of hIAPP aggregation by about threefold. These findings provide evidence for the intrinsic ability of Cu^{2+} ions to stabilize hIAPP in its native, non-toxic random coil conformation, which prevents amylin from aggregating after the β-sheet motifs are formed. The binding of Cu^{2+} ions to amylin also reduces its ability to induce apoptosis and to form a low affinity complex with hIAPP, displaying low pro-oxidative activity in vitro and in cells [60].

Several different experimental techniques as well as Constant Temperature Molecular Dynamics (CTMD) simulations have been applied to the hIAPP by Sinopoli et al. [22], in order to estimate its conformation in the presence and absence of copper(II). Results showed that both the fiber structure and aggregation kinetics of hIAPP have been extremely affected by Cu(II) ions, as well as its tendency to be degraded by proteases (Fig. 2). Specifically, MS data show an equilibrium between two conformations of hIAPP, with the more flexible state being the most dominant. On the other hand, results obtained by Circular Dichroism (CD) spectra of hIAPP are in accordance with a random coil conformation, and that the aggregation can be formed via incubation of the peptide alone. The structurally compacted conformer is formed due to the presence of copper ions, and will be eventually the only existing structure. However, by using spectroscopic patterns, the authors found that there are no clear signs of β-sheet conformation recorded in the presence of copper(II) ions, thus these observations suggest that hIAPP fibril formation can be inhibited the metal ion. The copper(II)-hIAPP complexes are less exposed to enzyme and metalloprotease degradation, indicating that the binding site of the metal occurs within the (17–29) hIAPP region. The coordination modes of this fragment are still in progress. Mixed parallel/antiparallel arrangements are indicated by the solid-state NMR as well as CTMD simulations, providing evidence for the randomness of the copper(II) ion-induced aggregation process.

The binding stoichiometry of hIAPP–Cu^{2+} complexes was studied as a function of Cu^{2+} concentration by using Laser Ablation Electrospray Ionization (LAESI) on samples with different concentrations of Cu^{2+}. The results indicated a binding stoichiometry with a 1:1 ratio between the peptide and the metal ions for all of the Cu^{2+} concentrations, even when there was a twentyfold excess of Cu^{2+} ions [8].

Further studies [62,63] showed that in peptide fragments of rat amylin inclusion of the –19SSNN22– sequence is necessary for copper ion binding at neutral pH range. Deprotonated amide nitrogen atoms are exclusively involved in metal binding, with the side chain amide group of asparagine being the primary binding site. The anchoring role of the amino group was dominant in the presence of free amino terminus, but there was additional stabilization from the –19SSNN22– sequence observed. Moreover, it was also found by David et al. [38] that the –17VRSSNN22–NH2 sequence as *N*-terminally free hexapeptide can form stable dinuclear copper ion complexes in which the amino terminus and the fragment –19SSNN22– sequence are considered as the binding sites of the metal. These results provide evidence that internal positions of IAPP, including asparagine and surrounding polar side chains, can act as anchors for the coordination of copper(II) ions [38], even in the absence of histidine, which is a strongly coordinating side chain [64]. Sanchez-Lopez et al. [65] performed a spectroscopic study of the binding of Cu^{2+} ions to hIAPP (18–22) residues using several techniques, e.g., Electron Paramagnetic Resonance (EPR), NMR, electronic absorption, and CD. Their results showed that Cu^{2+} ions bind to the imidazole N1 of His18, and to the deprotonated amides of Ser19 and Ser20. There are two ways to provide the oxygen-based ligand of Ser20, either via its hydroxyl group or its backbone carbonyl, while N22 may also play a role as an axial ligand. Ser20 was found to stabilize the coordination of the Cu^{2+} ions toward the C-terminal. Moreover, the role of copper(II) ions in the aggregation of hIAPP, which is directly connected to the histidine binding, is further supported by the fact that in rIAPP sequence the His18 is replaced by arginine residue, and the rat amylin fragments are not susceptible to aggregation [66].

4. Iron(II) ions

Mukherjee et al. [36] used different spectroscopic techniques, such as absorption, resonance Raman (rR), and EPR, on various lengths ((1–37), (1–19), (1 − 22), and (20–37)) of hIAPP to confirm that iron in the form of heme can bind to hIAPP. They also investigated the active-site environment of heme-hIAPP complexes. To determine the heme binding domain, two different fragments of hIAPP have been chosen: The hydrophilic (1–19) fragment and the amyloidogenic (20–37) fragment. hIAPP(1–19) has three residues known to bind heme in the native conditions. It was shown that His18 residue and the two cysteine residues (Cys2 and Cys7) are able to bind to heme in several different proteins, i.e., hemoglobin, myoglobin, cytochrome *c* oxidase and others, as well as cytochrome P450, nitric oxide synthase, etc. However, since the thiolate groups of both cysteine residues are oxidized and together form a disulfide bridge, they are no longer able to coordinate heme. Further, the amyloidogenic fragment contains another residue that is known to act biologically as a binding site for heme in catalase, the tyrosine residue Tyr37. Thus, several specific site mutants of hIAPP (1–19) were considered to determine the residue that act as a heme binding site. The single mutations His18Gly and His18Asn were used for the examination of histidine coordination, while single mutation Arg11Asn, double mutation Arg11Asn; His18Asn were used to identify the effects of both Arg11 and His18. Finally the hIAPP(1–22) fragment was tested against the coordination of heme coordination without the disulfide bridge. In the same study, Mukherjee et al. [36] found that heme is able to bind to two peptides, native hIAPP(1–37) and hIAPP (1–19), by examining the absorption spectra. However, hIAPP(20–37) incubated with heme shows a spectrum that is identical to that of free heme, even after prolonged incubation, which indicates that heme is not able to bind to hIAPP(20–37). This provides evidence that the fragment (1–19) of the peptide sequence is where the heme binding residue lies, and eliminates the possibility of Tyr37 acts as heme binding residue. On the other hand, hIAPP(1–22) fragment, without the Cys2-Cys7-disulfide bridge, also shows spectral changes similar to native hIAPP(1–19). Thus, this possibly indicates that heme does not coordinate to the cysteine residues as the native peptide-heme complex and the heme complex of the fragment without the disulfide bridge (which has available thiolate groups of Cys for heme coordination) shows similar spectral features.

5. Nickel(II) ions

Nickel has been investigated in only one study, where David et al. tested Ni(II) for its ability to bind to rIAPP [38]. Potentiometric, UV–visible, CD, and NMR spectroscopic methods were used to study the Ni(II) complex of the *N*-terminal free peptide fragments of rIAPP: SSNN-NH2, SSNA-NH2, AANN-NH2, VRSSNN-NH2, and GGHSSNN-NH2. Their results indicated that the –19SSNN22– residues of the rIAPP cannot be the primary site for the anchoring of Ni(II) ions. However, an increased stability of the corresponding complexes revealed by the NMR measurements performed on the *N*-terminally free peptide SSNA-NH2, indicating that an equilibrium was reached between the common (NH2,3N–(peptide)) and (NH2,2N–(peptide),N–(asparagine))

coordination modes in basic solution. Ni(II) ions are well known for their ability to promote amide deprotonation and coordination in a significant high pH range [67,68]. For that, the peptide fragments that are *N*-terminally protected cannot form complexes with Ni(II) ions in a biologically relevant pH range (for human blood 7.35–7.45) [69].

It was also reported that nickel ions might damage insulin function and induce glucose metabolism deregulation through the ROS pathway [70,71]. Moreover, Gupta et al. [72] found that in rats nitric oxide synthase (NOS) levels can be increased by nickel ions, along with cyclic guanosine monophosphate, which might lead to hyperglycemia by stimulating endocrine secretion. However, whether these findings in animal models can explain the association of nickel ion exposure with diabetes in humans needs thorough investigation in the future.

6. Gold complexes

Gold complexes have remarkable effects on the aggregation of hIAPP (Fig. 2). Inhibitory effects on the fibrillization of hIAPP were applied by three gold complexes with different nitrogen-containing aromatic ligands: 1-[Au(bipy)Cl2][PF6] (bipy = 2,2′-bipyridine), 2-[Au(Ph2bpy)Cl2]Cl (Ph2bpy = 4-4′-diphenyl-2,2′-bipyridyl), and 3-[Au(phen)Cl2]Cl (phen = 1,10-phenanthroline). The study by Lei et al. [73], applied several experimental techniques such as the ThT fluorescence assay and AFM to examine different characteristic changes of hIAPP, while Dynamic Light Scattering (DLS) experiments were used to determine the particular effects of these gold complexes on protein aggregation. Electrospray Ionization-Mass Spectrometry (ESI-MS) and intrinsic fluorescence method were employed to investigate the binding properties between the gold complexes and hIAPP. By exploring the details of the binding site using NMR spectroscopy, Lei et al. found that complexes 2 and 3 strongly inhibited the aggregation of hIAPP, compared to a fluctuated effect displayed by complex 1 on the fibril formation at high concentration. The effects inhibiting protein aggregation were derived from multiple interactions, including the possible coordination between the gold and the histidine residue, ligand steric effects, and the π–π stacking interaction between the nitrogen-containing aromatic ligands and hIAPP aromatic residues. Moreover, gold complexes showed the ability to inhibit the aggregation of hIAPP through dimerization, stabilize hIAPP as monomers, and thus prevent further fibrillization of the peptide. Furthermore, gold ions showed a non-interchangeable effect on the assembly of the peptide.

Another study used similar techniques to investigate the interactions of the amyloid peptides PrP106-126 and hIAPP with two tetra-coordinated gold–sulfur complexes, dichloro diethyl dithiocarbamate gold complex and dichloro pyrrolidine dithio-carbamate gold complex [74]. The results showed that gold(III) complexes bind to amyloid peptides with high affinity via metal coordination and hydrophobic interaction. In that study, the binding was stronger with PrP106-126 than with hIAPP. Histidine residue may play an important role in the metal binding with both PrP106-126 and hIAPP. The metal coordination was notably exhibited by both of the gold(III) complexes, as found in the peptide–Au–ligand adduct. The amyloid peptide fibrils scattered into nanoscale particles when the peptide and gold complexes interacted, decreasing the level of amyloid peptide cytotoxicity. These results suggest that tetra-coordinated gold–sulfur complexes may inhibit amyloidosis-related diseases.

7. Ruthenium complexes

Mononuclear ruthenium (Ru) complexes were recently proven to inhibit the aggregation of hIAPP [75]. However, Gong et al. [76] found that binuclear Ru complexes have a greater ability to inhibit aggregation than the corresponding mononuclear Ru complexes (Fig. 2), possibly as a result of the second metal center in the binding of the monomeric species of amylin. The authors used a ThT assay to elucidate the effects of the Ru complexes on the aggregation of hIAPP. The ThT fluorescence intensity was high in the absence of Ru complexes, reflecting the fibrillation of hIAPP. After co-incubation with binuclear Ru complexes, the intensity of the fluorescence was drastically decreased. In addition, the concentration of Ru complexes also affects the inhibition of hIAPP aggregation [76]. A study by He et al. [75], where aromatic-containing Ru complexes were used, had the same approach as Gong et al. in that it used a ThT assay, Transmission Electron Microscopy (TEM), and Atomic Force Microscopy (AFM) to further confirm the inhibition of hIAPP aggregation by Ru complexes. The results proved that the inhibition of hIAPP fibril formation is due to the interaction of Ru complexes with hIAPP, and that Ru complexes also promote the disaggregation of formed fibril. Furthermore, NMR spectroscopy and Matrix-Assisted Laser Desorption/Ionization Time Of Flight Mass Spectrometry (MALDI-TOF MS) were used to study the interactions between the Ru complexes and hIAPP. The results indicate that Ru complexes induce conformational changes in hIAPP by binding to the peptide, both in metal coordination and in non-bonded interactions. Changes in the amide chemical shift of several residues, e.g., S20, L27, and S28, indicate that the C-terminal of the hIAPP could be involved in the binding of the Ru complexes. These conformational changes in hIAPP show that the lower fraction of the β-sheet structure of hIAPP occurs immediately after binding with the Ru complexes. Thus, it significantly reverses the aggregation of hIAPP [75].

Zhu et al. [77] investigated ruthenium polypyridyl complexes. Their results agree that Ru complexes cause the disaggregation of hIAPP fibrils into small nanoparticles. Furthermore, using MTT (3-(4,5)-dimethyl-2-thiazolyl-2,5-diphenyl-tetrazolium bromide assay), they found that Ru complexes are also capable of reducing the cytotoxicity induced by hIAPP in insulinoma cell line INS-1.

Ma et al., [78] used ThT assays to investigate the influence of four specific Ru complexes on hIAPP fibrillation. Information obtained from the decreased tyrosine intrinsic fluorescence and ThT fluorescence signals confirmed that Ru complexes inhibit the fibril formation of hIAPP [78]. In this study, the authors did not specify the binding mode between the Ru complexes and hIAPP at the atomic level.

8. Vanadium ions

Vanadium ions (V) have been known for their in vitro insulin-mimetic effects since 1979 [79,80]. Since then, V ions have been investigated for their potential in treatment of chronic diabetes [81–85]. As metal ions can affect the activities of amyloid peptides, some studies [86,87] have examined the effects of V complexes on hIAPP, and whether these complexes are able to inhibit the aggregation of hIAPP. He et al. [86] used different experimental techniques, like ThT, (AFM), (CD), and spectrofluorometric measurements, to test the effects of six V complexes, 1- ammonium (2,6-pyridine-dicarboxylic)dioxovanadate ($(NH_4[V(O_2)(dipic)])$; 2-bis(maltolato)-oxovanadium (BMOV); 3-bis (N′,*N*′-dimethylbiguanidato)-oxovanadium ($VO(metf)_2{\cdot}H_2O$); 4- potassium oxalatooxo-diperoxovanadate ($K_3[VO(O_2)_2(OX)]{\cdot}2H_2O$); 5-ammonium (2,2′-bipyridine)oxodiperoxovanadate ($(NH_4)[VO(O_2)_2(bipy)]){\cdot}4H_2O$); and 6-ammonium (1,10-phenanthroline)oxodiperoxovanadate ($(NH_4)[VO(O_2)_2(phen)]{\cdot}2H_2O$), on the hIAPP peptide. These six complexes and their derived active species interact either hydrophobically or electrostatically hIAPP to significantly inhibit aggregation. The V complexes have strong inhibitory effects on peptide aggregation due to their high binding affinity and large ligands. To confirm that the V complexes affected hIAPP-induced cytotoxicity, which has been associated with T2DM, changes in cell viability were investigated. The tests proved that V complexes protected INS-1 insulinoma cells well from cytotoxicity induced by hIAPP. The clinical drug BMOV had the greatest effect on reversing the aggregation and reducing cytotoxicity.

9. Interaction of IAPP with the cell membrane

Jha et al. [39] showed that His18 acts as an electrostatic switch, inhibiting fibrillization in its charged state, which is heavily pH-dependent. Moreover, His18 plays an intrinsic role in hIAPP binding to the cellular membrane [41]. The primary region that is responsible for the disruption of the membrane is the *N*-terminal region of hIAPP. When bound to the membrane, hIAPP(1–19) causes membrane disruption in a similar range as the full-length peptide, but without the formation of amyloid fibers [41]. The truncated rIAPP(1–19) fragment, which is both non-toxic to the cell and non-amyloid forming, has only one different amino acid from the human peptide: Arg18 in the rat variant while His18 in the human variant. A previous study [2] has measured the effects of the fragment (1–19) of rIAPP and hIAPP on islet of Langerhans and model membranes to explain the effect of the difference in the amino acid residue. Authors noticed that the levels the intracellular calcium of islets cells significantly increased with the addition of hIAPP(1–19), which indicate that the cellular membrane has been disrupted. rIAPP(1–19) peptide had significantly less effect on the membrane, and it showed reduced ability to penetrate β-cell membranes [2,88]. Dye leakage assays and (CD) experiments on model liposomes showed that at low peptide to lipid ratios the rIAPP(1–19) is unable to bind to or disrupt lipid membranes, indicating that the aggregate formation necessary for membrane binding and disruption is dramatically less in the rIAPP(1–19) than hIAPP (1–19). In contrast, at pH 6.0, where His18 is protonated, hIAPP(1–19) resembles rIAPP(1–19) in its limited ability to cause membrane disruption. Furthermore, using differential scanning calorimetry, the authors found that rIAPP(1–19) has a different binding mode to the membrane compared to hIAPP (1–19). The later peptide shows a minor effect on the phase transition of lipid vesicles, suggesting a membrane peptide orientation in which the acyl chains mobility of the membrane is practically unaffected. However, at low concentrations, rIAPP(1–19) shows a strong impact on the phase transition of lipid vesicles, suggesting that is not easy for the peptide to be inserted into the membrane after binding to the surface. The given results indicate that the modulation of the peptide orientation in the membrane by His18 can be the primary reason for the toxicity of non-amyloidogenic forms of hIAPP [2]. The aggregation properties of amylin are very much dependent on the positions of residues other than His18. In 1990, Westermark et al. [66] claimed that positions 25, 29, and especially 28 are important for the properties of amylin aggregation. These findings are in line with the fact that in rIAPP, in contrast to hIAPP, these positions are occupied by proline residues that do not favor β-sheet formation.

The results of Ramamoorthy's group [41] indicate that it is not necessary for hIAPP to form amyloid fibers in order to disrupt the membrane. Previous studies [9,89] proved that amyloid fibers themselves are not particularly toxic, but there is controversy as to whether the process of amyloid formation is necessary for the amyloid peptides to generate toxic intermediates and disrupt the membrane. Ramamoorthy's group suggest that hIAPP disrupts the membrane without the formation of amyloids, and that membrane disruption occurs primarily as a consequence of factors not necessarily related to amyloidogenesis [90]. As mentioned before, rIAPP and non-amyloidogenic peptide variants of amylin are non-toxic, providing evidence that the formation of amyloids is primarily responsible for the cytotoxicity of hIAPP. However, Knight et al. [91] recently showed that rIAPP exhibits some membrane-disrupting activity. Also, diabetic rats show a small degree of β-cell apoptosis, which supports the conclusion that rIAPP can be toxic, though much less so than hIAPP [92].

Other amyloid peptides also have the ability to form channels; therefore, Patel et al. [93] used planar lipid bilayers and Atomic Force Microscopy to test the 441-amino-acid htau40 isomorph of the Tau protein for its ability to form ion-permeable channels. Results showed that the Tau protein is only capable of forming ion channels under acidic conditions. These Tau protein channels are remarkably similar to the channels formed by amyloid β (Aβ)-peptides in terms of appearance, physical and electrical size, permanence, lack of ion selectivity, and multiple channel conductance. On the other hand, they have some differences from amyloid channels, such as their voltage dependence and resistance to blockade by zinc ions. Also, the channels formed by Tau proteins are not blocked by $Zn2+$ ions, even at higher $Zn2+$ concentrations (up to 1 mM), unlike the channels that are formed by other Aβ-peptides [93]. Furthermore, α-synuclein also has the ability to form membrane-ion channels, but further investigation is needed to determine which metal ions may directly influence this process.

Some of metal ions have been tested only with specific short fragments of IAPP peptides; therefore, future studies are required to examine the effects of metal ions on the full-length peptide. Another direction of future study should be in vivo experiments on the impact of metal ions on the formation of soluble amylin oligomers and on the glucose-tolerance mechanisms observed in transgenic mice with overexpressed amylin in the pancreatic cells.

In addition, hIAPP share similarities with Aβ amyloid peptide in terms of aggregation features, metal ions and membrane interactions. It was also reported that there is an interaction between rIAPP and the membrane. [94,95] Moreover, the presence of small aggregates can be confirmed also in rIAPP samples, therefore, an rIAPP-associated cytotoxicity could be conceivable. Mentioned results suggest that the issue of potential rIAPP toxicity needs further investigation.

10. Conclusion

The interactions of metal ions with amylin (IAPP) affect its chemistry and structural properties. The coordination mode and the effects caused on the IAPP peptide by interaction with seven metal ions, zinc, copper, iron, nickel, gold, ruthenium, and vanadium are discussed in this review. Interaction of these metal ions with amylin may affect its structure, causing formation of misfolded IAPP, which can undergo fibril formation, finally resulting in generation of oligomeric forms like protofibrils and mature fibrils. Fe(II), Cu(II), and Zn(II) ions promote the formation of amylin oligomers/protofibrils. Ru complexes, V complexes, and some of the Au(III) complexes examined inhibit the formation. Nevertheless, for Au(III) complexes, the nature of their effect on fibril formation can heavily depend on concentration. Cu(II) ions also may inhibit amylin fibrillation and reduce toxicity. The influence of metal ions on the amyloid pore formation by amylin and other amyloidogenic peptides, is thus complex and will need to be studied in more details.

The importance of metal ions and their complexes with biomolecules in the medical applications brought much attention to this field, because metal ions can be used for diagnostic and treatment purposes in medical application. Moreover, as explained by all of reviewed studies they also have a significant role in case of the diabetic patients. This suggests that we can benefit from specific metal ions in the diagnosis or even treatment of diabetes. Thanks to the exploring of the interaction of metal ions and the biologically important biomolecules, new ways for the developing of new alternative medical treatment strategies can be opened.

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