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Review paper

Human islet amyloid polypeptide: A therapeutic target for the management of type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and other metabolic disorders are often silent and go unnoticed in patients because of the lack of suitable prognostic and diagnostic markers. The current therapeutic regimens available for managing T2DM do not reverse diabetes; instead, they delay the progression of diabetes. Their efficacy (in principle) may be significantly improved if implemented at earlier stages. The misfolding and aggregation of human islet amyloid polypeptide (hIAPP) or amylin has been associated with a gradual decrease in pancreatic β-cell function and mass in patients with T2DM. Hence, hIAPP has been recognized as a therapeutic target for managing T2DM. This review summarizes hIAPP's role in mediating dysfunction and apoptosis in pancreatic β-cells via induction of endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, inflammatory cytokine secretion, autophagy blockade, etc. Furthermore, it explores the possibility of using intermediates of the hIAPP aggregation pathway as potential drug targets for T2DM management. Finally, the effects of common antidiabetic molecules and repurposed drugs; other hIAPP mimetics and peptides; small organic molecules and natural compounds; nanoparticles, nanobodies, and quantum dots; metals and metal complexes; and chaperones that have demonstrated potential to inhibit and/or reverse hIAPP aggregation and can, therefore, be further developed for managing T2DM have been discussed.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with hyperglycemia, elevated levels of glucose in plasma for prolonged periods, and development of insulin resistance (IR) in the target tissues [1]. Furthermore, owing to the persistent increase in nutrient load, metabolic imbalance occurs with a gradual decline in the function and mass of pancreatic β-cells [2]. In addition, T2DM poses a significant risk for life-threatening disorders such as cardiovascular diseases, including coronary heart disease, stroke, and heart failure [3]; acute renal failure and kidney disorders [4]; blindness [5]; cancers such as liver, pancreas, lung, and colorectal; and other diseases such as liver disease [6] and chronic obstructive pulmonary disease [3].

The incidence of T2DM has reached epidemic proportions globally. According to the International Diabetes Federation (IDF; https://www.idf.org/), approximately 536.6 million people were estimated to have diabetes in 2021. The IDF predicts these numbers to significantly increase globally (approximately 643 million by 2030 and 783 million by 2045, respectively) [7]. This increase is alarming, particularly in adolescents (aged 12–19 years) and young adults in whom the prevalence rate is 3.3%–14.3% for undiagnosed prediabetes and 0.1%–2.2% for confirmed T2DM [8]. This increase in the prevalence rate has been associated with factors such as changes in diet, lack of physical activity, sedentary lifestyle, overnutrition, and stress [8,9]. Currently, T2DM is one of the top 10 causes of death in adults globally [10].

T2DM, similar to other metabolic disorders, is a silent disease that often goes unnoticed in patients because of unavailability of suitable biomarkers that can be used for early diagnosis and prognosis. The currently used therapeutic regimens aim to slow the progression of T2DM and are unsuccessful in reversing it. Thus, if these drugs are implemented at earlier stages, much before the development of metabolic syndrome, their efficacy can be increased in principle. Along these lines, the human islet amyloid polypeptide (hIAPP) or amylin has been recognized as a therapeutic target for T2DM management [11,12]. This review

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summarizes the current understanding of the role of hIAPP in mediating pancreatic β-cell dysfunction and death, thereby leading to the development of T2DM. Furthermore, it discusses the current therapeutic regimens available for T2DM management, possibility of using intermediates of the hIAPP aggregation pathway as potential drug targets, and different therapeutic interventions targeting hIAPP, which can be further developed for managing T2DM.

2. hIAPP and T2DM

T2DM is characterized by hyperglycemia, hyperlipidemia (in T2DM complicated with obesity), and elevated glycated hemoglobin A1c levels, characteristics associated with a gradual decrease in pancreatic β-cell function and mass [13,14]. Defects in the production, secretion, and signaling of insulin, the primary hormone produced by pancreatic β-cells, lead to the development of IR in target tissues, including skeletal muscles, adipose tissues, and liver [15]. In addition to insulin, the β-cells synthesize another important hormone, i.e., hIAPP, which colocalizes with insulin in the secretory granules [16]. Under normal physiological conditions, hIAPP and insulin secretion occurs postprandially at a ratio of 10–100:1 (insulin:amylin) in response to various stimuli, including glucose [17]. The released hIAPP enters the systemic circulation, crosses the blood-brain barrier, and activates specific receptors in the brain, inducing satiety. Moreover, it plays a pivotal role in suppressing the release of glucagon from the pancreas [18]. The interplay between glucagon and insulin significantly contributes to the maintenance of glucose homeostasis [19]. Hyperproduction and hypersecretion of hIAPP are observed in hyperglycemic conditions associated with diabetes [11]. A study conducted using pancreatic β-cells from hIAPP-transgenic mice has shown that hIAPP overexpression inhibits insulin secretion through an autocrine effect [20]. In addition, the exposure of β-cells to high glucose and free fatty acids, including palmitate and oleate, activates the IAPP promoter, increases its expression and release, and significantly decreases the insulin mRNA levels. Palmitate exposure leads to the degradation of carboxypeptidase E, an exopeptidase that processes the C-terminal of the hIAPP peptide, in a dose-dependent manner [21]. Thus, under diabetic conditions, instead of following a canonical pathway of processing and secretion, aberrantly processed hIAPP tends to misfold and produce aggregates, oligomers, and fibrils, forming deposits and plaques in the islets of Langerhans [22,23]. Such plaques have been reported in the pancreata of humans and other primates, including *Macaca mulatta* (macaques) and *Mandrillus sphinx* (monkeys), and associated with pancreatic β-cell dysfunction and death [11,24,25]. Similar to hIAPP, proteins such as α-synuclein misfold and produce aggregates in the brain of patients with Parkinson's disease. Tau protein and amyloid-beta (Aβ) have shown similar implications in patients with Alzheimer's disease [26]. Preliminary in vitro studies have exhibited cross-reactivity between hIAPP and other amyloidogenic proteins, including α-synuclein, tau protein, and Aβ; however, these studies are at their early stages and require further validation [27].

Deposition of hIAPP aggregates has been observed in red blood cells (RBCs) [28] and other essential human organs such as the heart [29,30], kidney [31], brain, and eyes [32,33]. A previous study on hIAPP-transgenic Sprague-Dawley rats has shown that hIAPP deposition disrupts the structure and function of cardiac myocytes [30]. In addition, it promotes sarcolemmal injury, forms adducts with reactive aldehydes, and upregulates the proinflammatory cytokine interleukin-1β (IL-1β) levels, independently of hyperglycemia, in hIAPP-transgenic rats [29]. hIAPP aggregates interact with Aβ peptide and promote its aggregation in the brain, thereby promoting diabetes-related dementia [33]. These aggregates have also been observed in the renal tissue biopsies, primarily spread across the expanded mesangial area, Bowman's capsule, Kimmelstiel-Wilson nodules, and blood vessels of patients with diabetic nephropathy and have been associated with disease severity [31]. Recent evidence suggests that hIAPP-coated RBCs exhibit an altered shape and decreased functional hemoglobin level [28].

3. hIAPP aggregation leads to loss and dysfunction of pancreatic β-cells

Studies on patients with diabetes from various populations (from Korea, Japan, the United Kingdom, and Belgium) have reported approximately 30%–60% decrease in the mass and volume of pancreatic β-cells when compared with those in individuals without diabetes [34–38]. This decrease is a prolonged process that appears to start nearly 10–12 years before the actual diagnosis of T2DM [39,40]. Recent reports have revealed that this decrease in the mass and volume of β-cells is not a consequence of apoptosis alone [38] but can also be attributed to the process of de-differentiation, loss of β-cell identity [41]. Studies on macaques and domestic cats have demonstrated that the deposition of IAPP leads to β-cell dysfunction and T2DM [42,43]. Amyloid aggregates have been detected in the pancreas of patients with T2DM [38,44]; however, these deposits have also been detected in microscopic proportions in aged individuals without diabetes [45].

hIAPP monomers are classified as intrinsically disordered proteins and/or aggregation-prone proteins [46]. hIAPP is synthesized as a prepropeptide, comprising 89 amino acids. Proteases further process this prepropeptide in the endoplasmic reticulum (ER) to form a propeptide comprising 67 amino acids, which undergoes posttranslational modifications to produce 37 amino acid long, mature hIAPP peptide [47]. The mature hIAPP peptide is moderately hydrophobic and does not contain acidic amino acids (Fig. 1A). However, it possesses a few positively charged amino acid residues such as Lys-1, Arg-11, and His-18 (as per the pH); a disulfide bond between Cys-2 and Cys-7; and an amidated C-terminal. Thus, hIAPP acquires a positive charge at the physiological pH [48]. Compared with the human isoform, the presence of three proline residues at positions 25, 28, and 29 in rodent IAPP makes it nonamyloidogenic [16]. The hIAPP aggregation pathway follows a sigmoid-shaped curve [49] and is divided into three distinct phases: lag, log, and plateau/saturation. The lag phase starts when two structurally disordered monomers interact to produce a dimer, after which there is continuous addition of more monomers to form oligomers. This process is known as primary or homogenous nucleation [49,50]. Eventually, these oligomers serve as a seed for the formation of higher-order soluble oligomers and insoluble fibrils (Fig. 1B). In silico analyses have indicated a transition of α-helix to β-sheet, leading to the formation of hexamers, which further assemble to form intermediate β-barrel structures, followed by the formation of cross-β fibrils [51]. The high energies of β-rich oligomers promote the nucleated conformation of oligomers, accelerating the aggregation process [52]. Once fibrils are established, they facilitate the formation of new fibrils in a process known as secondary or heterogeneous nucleation [53,54]. The elongation and growth of fibrils are accelerated in the log phase wherein the oligomers undergo conformational transitions to form β-sheets [46,55]. Finally, in the saturation phase, these β-sheets are organized as proto-fibrils and amyloid fibrils, i.e., partially ordered, fibrillar protein aggregates rich in the β-sheet structure in

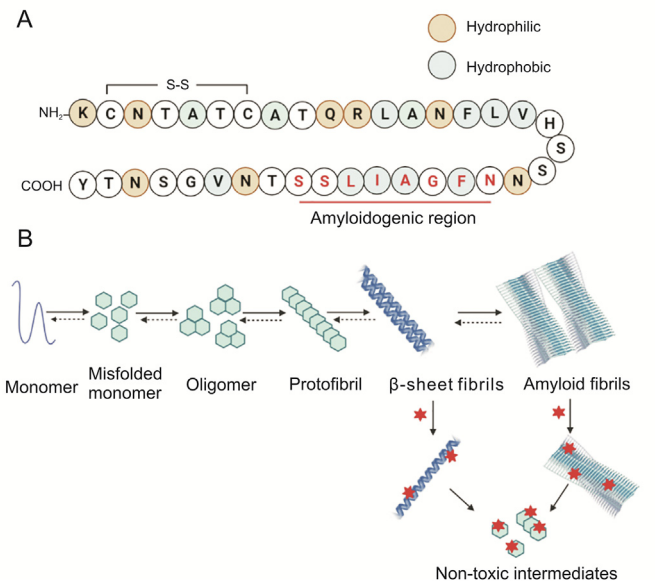

Fig. 1. Human islet amyloid polypeptide (hIAPP) structure and intermediates of the aggregation pathway. (A) hIAPP comprises 37 amino acids. The amyloidogenic region has been indicated in red. (B) Various intermediates of the hIAPP aggregation pathway can be targeted using inhibitors (indicated by red stars), which potentially reverse the process. The fibrils and amyloidogenic aggregates can be converted into nontoxic intermediates by these inhibitors.

a characteristic cross-β conformation [56]. The structural characteristics of hIAPP have previously been described in detail [57]. Initially, hIAPP fibrils were considered to be primarily responsible for mediating cytotoxicity; however, it was later confirmed that among the different intermediates, small oligomers form the most toxic species. Thus, the inhibition of toxic oligomer and/or fibril formation at early stages may effectively suppress hIAPP-mediated cytotoxicity [51,58,59]. hIAPP oligomers have been detected in hIAPP-transgenic mice using anti-IAPP antibodies and the amyloid-specific stain thioflavin S (Fig. 2) [60]. hIAPP mediates toxicity in various manners such as by inducing ER stress [61], oxidative stress [62], mitochondrial dysfunction [63], inflammatory cytokine secretion [64], and autophagy blockade [65]. The following subsections briefly discuss these mechanisms.

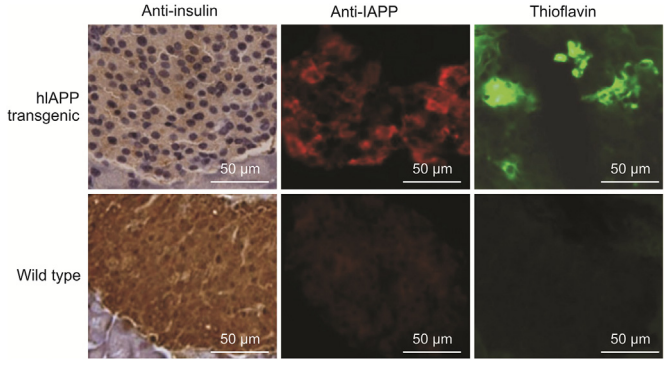

Fig. 2. Representative sections of the pancreatic tissue from hIAPP-transgenic and wild-type mice. Increased staining with anti-IAPP and thioflavin S is observed in sections obtained from the transgenic mice compared with that from the wild-type controls. (Reprint from Ref. [60] with permission.)

3.1. Induction of ER stress

Toxic pro-IAPP and IAPP oligomers have been reported in multiple locations of the secretory pathway (ER, Golgi, and secretory vesicles) [23]. The accumulation of misfolded or unfolded hIAPP in the ER lumen activates the unfolded protein response [66], leading to the degradation of these misfolded proteins by the ubiquitin-proteasome system [67]. Studies conducted on the rat insulinoma cells (INS-1E) overexpressing hIAPP have demonstrated increased levels of polyubiquitinated aggregates [68] and decreased levels of the deubiquitinating enzyme ubiquitin carboxyl-terminal hydrolase (UCH-L1) [67]. Furthermore, the shortage of UCH-L1 reportedly promotes hIAPP-mediated cytotoxicity [69]. The hIAPP-induced ER stress can be alleviated with endogenous chaperones, for example, binding immunoglobulin protein, protein disulfide isomerases, and/or chemical chaperones such as tauroursodeoxycholic acid or 4-phenylbutyric acid (4-PBA) [68]. Intracellular hIAPP oligomers pass through the lipid bilayer within the secretory pathway, enhancing its permeability and thus increasing Ca^{2+} influx in the cytosol, which is a signal for the intrinsic pathway of apoptosis [23]. Reduced levels of Ca^{2+} in the ER lumen influence the functioning of molecular chaperones, leading to the accumulation of misfolded proteins that amplify oxidative stress in the ER [70]. Persistent ER stress induces apoptosis in pancreatic β-cells [61,67].

3.2. Induction of oxidative stress

The formation of hIAPP amyloidogenic aggregates is associated with increased oxidative stress in pancreatic β-islets. Significantly higher levels of oxidative stress markers such as nitrotyrosine and 8-hydroxydeoxyguanosine have been reported in the pancreatic islets of patients with T2DM than in those of healthy controls [71]. The exposure of INS-1E cells to hIAPP correlates with reduced expression of antioxidant genes (e.g., catalase, superoxide dismutase 1 (Sod1), and glutathione peroxidase (Gpx)) and increased expression of apoptotic genes (e.g., caspase-3 and Bcl-2 associated X-protein (Bax)) [72]. Similar studies using INS1E823/13 cells overexpressing hIAPP have demonstrated that hIAPP creates hypoxia-like conditions in these cells and leads to the activation of the hypoxia-inducible factor α/6-phosphofructo-2-kinase-fructose-2,6-bisphosphatase 3 pathway. Thus, a metabolic shift occurs when there is an upregulation of glycolysis and a downregulation of the tricarboxylic acid cycle. Consequently, similar to cancer cells, these cells show the Warburg effect where there is a shift from pyruvate to lactate metabolism, which then leads to the dysfunction of pancreatic β-cells [73].

It has been proposed that the reactive oxygen species (ROS) formed under diabetic conditions induces unfolding of the tightly folded native hIAPP. Once unfolded, hIAPP forms antiparallel crossed β-pleated sheet structure [74]. hIAPP-induced oxidative stress triggers the c-Jun NH_2-terminal kinase (JNK) pathway by activating apoptosis signal-regulating kinase-1 (ASK1) while decreasing the intracellular reduced glutathione levels. ASK1 activation correlates with hIAPP aggregate formation and T2DM progression [75]. Studies using the rat insulinoma (RIN)-m5F cell line and pancreatic islets derived from human cadavers show that ASK-1 inhibition (by ASK1 inhibitor 2,7-dihydro-2,7-dioxo-3H-naphtho (1,2,3-de)quinoline-1-carboxylic acid ethyl ester or thiol antioxidants) decreases the activation of hIAPP-induced ASK1 and JNK and thus leads to the reduction of cytotoxicity in these cells [75]. hIAPP exposure also blocks the nuclear factor erythroid 2-related factor 2 dependent antioxidant protective pathway, triggering apoptosis in pancreatic β-cells [76].

Treatment with antioxidants such as catalase, *n*-propyl gallate, *N*-acetyl-L-cysteine, reduced glutathione, and dithiothreitol is effective in combating oxidative stress, thus inhibiting apoptosis in pancreatic β-islets [77].

3.3. Disruption of mitochondrial network dynamics

Toxic hIAPP oligomers, which slip away from secretory pathways, puncture mitochondria and, in turn, disrupt the membranes by removing lipids from the lipid bilayer, a phenotype that is promoted by high levels of cytosolic Ca^{2+} [23,78]. This causes disruption of electron transport chain complexes and reduced ATP formation, leading to the production of ROS [79]. hIAPP-transgenic rats exhibit approximately 30% decrease in the oxygen consumption rate and a significant increase in the extracellular acidification rate compared with wild-type rats, clearly indicating that hIAPP induces oxidative stress [73]. The analysis of proteins playing a pivotal role in maintaining the dynamics of mitochondrial morphology substantiates the effects of hIAPP on the mitochondrial network. The expression of proteins involved in mitochondrial fusion, such as mitofusin 2 and optic atrophy-1, reportedly decreases, whereas that of proteins involved in mitochondrial fission, such as dynamin-1 like protein, increases [73,80]. Fluorescence and electron microscopic images of hIAPP-expressing rat insulinoma cell lines and islets from patients with diabetes display fragmentation and perinuclear distribution of the mitochondrial network in response to hIAPP [73,80]. Using INS-1E cells overexpressing hIAPP, a previous study has revealed that PTEN-induced kinase 1, a prime protein essential for the effective clearance of damaged mitochondria, is not processed by presenilins-associated rhomboid-like protease but accumulates in the outer membrane, indicating defective mitophagy [80]. hIAPP activates pro-oxidative activity and expression of plasma membrane-associated NADPH oxidase (NOX) and its regulatory subunits [75]. Brief exposure of hIAPP (in nanomolar concentrations) to RIN-5F cells increases the expression of the receptor for advanced glycation end products (RAGE). hIAPP aggregates bind at the RAGE to trigger the anti-oxidant defense (hermetic response) by increasing the levels of NOX, catalase, and Gpx [81]. siRNA-mediated knockdown and inhibition of NOX via selective NOX inhibitors, ML171 and apocynin in rat insulinoma cell lines INS-832/13 and RIN-5mF, markedly decrease the mitochondrial stress [75]. hIAPP-induced stress triggers the JNK pathway, further recruiting various proapoptotic molecules. The release of cytochrome-c from mitochondria and increased levels of Bcl-2-like protein 11 (commonly known as Bim), Fas/Fas-associated protein with death domain, caspase-8, Bax, and proteolytic caspase-3 proteins suggest that apoptosis occurs through both intrinsic and extrinsic pathways [63,72,79,82,83]. Treatment of INS-1E cells with phycocyanin, a photosynthetic pigment from blue-green algae that possesses anti-oxidant properties, reinstates hIAPP-induced mitochondrial dysfunction via ROS inhibition [63].

3.4. Impairment of autophagy

Autophagy is an important mechanism that plays an important role in mediating protection against hIAPP-induced cytotoxicity [65,84]. hIAPP aggregates have been detected in the pancreatic β-islets of hIAPP-transgenic mice deficient in autophagy and are directly associated with the occurrence of T2DM in these models. INS-1E cells overexpressing hIAPP show hyperactivation of the mammalian target of rapamycin (mTOR) pathway, an autophagy inhibitor, followed by the phosphorylation of Unc-51-like kinase, which obstructs the autophagy degradation pathway [80]. Electron micrographs of hIAPP-transgenic mouse islets and INS-1E cells overexpressing hIAPP show the accumulation of autophagosomes in these cells [85]. Elevated expression of proteins involved in the autophagy degradation pathway, microtubule-associated protein light chain 3B–II and p62, has also been reported [76,85]. Studies with hIAPP-transgenic mice elucidated that UCH-L1 enzyme deficiency enhances hIAPP-induced cytotoxicity by augmenting autophagy impairment [69]. Treatment with rapamycin, an inhibitor of the mTOR pathway, is associated with significant improvement in the function and viability of pancreatic β-cells [76,80]. hIAPP-transgenic mice fed with trehalose in addition to a high-fat diet for 4 weeks reportedly show an improvement in the impaired glucose tolerance and a significant increase in the insulinogenic index compared with control (phosphate buffered saline treated) mice. Trehalose treatment facilitates the clearance of hIAPP species via promotion of autophagy, thereby improving the function and viability of pancreatic β-cells [86].

3.5. Induction of islet inflammation

A population-based study conducted among patients with diabetes in Japan has stated that the loss of volume density of pancreatic β-cells in T2DM is associated with the presence of hIAPP amyloids and increase in macrophage infiltration [87]. Another study using pancreatic islets from hIAPP-transgenic mice has reported the co-existence of hIAPP amyloids and macrophages [88]. hIAPP oligomers induce the secretion of IL-1β from macrophages, subsequently leading to islet inflammation [88]. In addition to IL-1β, hIAPP increases the expression of other inflammatory cytokines such as chemokine (C–C motif) ligand 2 (CCL2); tumor necrosis factor-α; IL-1α; IL-6; CCL3; chemokine such as C–X–C motif ligand (CXCL)1, CXCL2, and CXCL10; and inflammasome markers such as NACHT, LRR and PYD domains-containing protein 3 (Nlrp3), PYD and CARD domain containing, and caspase 1 [64,89]. Electron micrographs of the islets of hIAPP-transgenic mice show the presence of hIAPP in the lysosomes of resident macrophages, suggesting impaired phagocytosis [90]. Furthermore, the contribution of phagolysosomes in hIAPP-induced islet inflammation has been confirmed in vitro in a previous study that reported that inflammasome activation in macrophages can be inhibited by cytochalasin D and bafilomycin A [88]. On one hand, these phagocytic cells are required for extracellular hIAPP clearance; they are also responsible for mediating inflammation and dysfunction in pancreatic β-cells on the other [91]. The role of resident macrophages in inflammasome activation has been demonstrated wherein clodronate-liposome-mediated depletion of islet macrophages in hIAPP-overexpressing mice has been associated with improved glucose tolerance and inhibition of proinflammatory gene expression even with increasing amyloid formation in the islets [91].

Prefibrillar (and not fully aggregated) hIAPP aggregates induce pro-IL-1β synthesis and IL-1β secretion through Toll-like receptor-2, whereas fibrillar hIAPP aggregates induce IL-1β secretion through Nlrp3 inflammasome activation [92]. The significance of IL-1β signaling in hIAPP-induced inflammation has been verified via the transplantation of hIAPP-expressing islets into diabetic non-obese diabetic (NOD)/severe combined immunodeficiency mice. These mice were treated with IL-1β receptor agonist (IL-1Ra); after 8 weeks of transplantation, they exhibited improved glucose tolerance, significantly increased macrophage number, and decreased amyloid deposition in vivo [64]. A similar protective effect of IL-1Ra has been demonstrated in obese Avy-$hIAPP^{Tg/0}$ mice [93]. A study using hIAPP-transgenic mice and

human islets has revealed that IL-1β induces Fas upregulation, caspase-8 activation, and Fas-mediated apoptosis [94]. In addition, IL-1β promotes pro-hIAPP misprocessing and amyloid formation. The treatment of these islets with anakinra, the recombinant form of IL-1Ra, reduces IL-1β, thereby reducing Fas expression and preventing apoptosis [94]. Akt/protein kinase B (PKB) signaling is important for the survival and growth of pancreatic β-cells [95,96]. A study with hIAPP-transgenic mice islets and human pancreatic islets from diabetic cadavers has shown that hIAPP decreases the levels of phosphorylated PKB and increases IL-1β expression in β-cells. Blocking IL-1β signaling with anakinra or exenatide (glucagon-like peptide-1 receptor agonist) normalizes the phospho-PKB levels, thereby improving the survival rate of islets [97].

3.6. Destabilization of the lipid bilayer

The plasma membrane of pancreatic β-cells comprises anionic phospholipids (approximately 2%–13%), cholesterol, gangliosides, and sphingomyelins [98]. This membrane is asymmetric because the inner layer is enriched with anionic lipids and the outer layer with sphingomyelin. All intermediates of the hIAPP aggregation pathway, including monomer [99], oligomer, fibrils, and higher-order amyloid structures, destabilize the membranes of pancreatic β-cells to various extents [100]. The damage fundamentally depends on the concentration of hIAPP and composition of the lipid bilayer [101–104]. Structural analysis using spectroscopic techniques has shown that at low concentrations, the binding of hIAPP monomer within the headgroup region spreads across the lipid bilayer to avoid leakage or damage to the ordered structure of membrane lipids. On the other hand, at high concentrations, hIAPP monomers adopt the β-sheet conformation forming aggregates, which bind to the surface of lipid instead of the headgroup and lead to membrane disruption through electrostatic and hydrophobic interactions [99,105]. hIAPP oligomers generate distinct pores in the membrane by forming ion channels or rupturing the lipid bilayer [106,107]. hIAPP fibrillation at the lipid bilayer destabilizes the membrane in a detergent-like manner, causing membrane thinning, fragmentation, and increased membrane conductance [108–110]. Phospholipids in the lipid bilayer are taken up in the process of amyloid formation [111], a process that is enhanced by Ca^{2+} disequilibrium [78,112]. This membrane perturbation leads to enhanced membrane permeability, ion exchange dysregulation, cytosol leakage, and oxidative stress generation in pancreatic β-cells [100]. A study conducted to evaluate the effect of membrane composition on hIAPP amyloid formation has demonstrated that anionic lipids enhance hIAPP amyloid formation and increase membrane permeability; zwitterionic lipids show no evident effects; and uncharged lipids increase the membrane order, thus reducing membrane leakage [101]. Cholesterol plays a vital role in clearing hIAPP toxic oligomers from the plasma membrane via (lipid-raft-like uptake) endocytosis [113] and reduces the rate of amyloid formation in vitro [104]. On the other hand, NaCl reduces hIAPP-membrane electrostatic interactions, thus decreasing membrane-mediated amyloid formation [104].

Using INS-1E cells and T2DM rats, a previous study has elucidated the combined action of lipids and hIAPP species in mediating pancreatic β-cell damage and apoptosis [114]. The disruption of the β-cell membranes releases intracellular hIAPP amyloids into the extracellular environment, which act as a starting point for the extracellular generation of hIAPP fibrils [16]. Intracellular hIAPP fibrils are formed as a result of a primary defect in the prohormone processing system, leading to the misprocessing of pro-IAPP at the ER [22,115]. When these misprocessed species are exposed to the extracellular environment, native hIAPP molecules secreted by surrounding β-cells add together and form extracellular amyloids [16].

3.7. Effect on extracellular matrix (ECM)

The ECM around the pancreatic islets plays a significant role in regulating their physiology, including survival, growth, and function [116]. A study conducted using mouse insulinoma β-TC3 cells has reported that proteoglycans synthesized and secreted by β-cells bind hIAPP and may be involved in amyloid formation [117]. Membrane-bound heparin sulfate proteoglycans play a pivotal role in extracellular hIAPP-mediated cytotoxicity by accelerating fibril formation [118]. Positively charged amino acid residues of hIAPP, such as Lys1, Arg11, and His18, are essential for the interaction between hIAPP and negatively charged sulfated proteoglycans of the ECM. Heparin, a glycosaminoglycan, binds to hIAPP cross-β structures and increases hIAPP fibrillation via electrostatic interactions. The rate of hIAPP fibrillation depends on the length of the heparin fragment; short heparin fragments (dp2–dp8) form a stable helix structure and inhibit hIAPP fibrillation, whereas longer fragments (dp20) do not affect fibrillation [119]. Heparin also reportedly enhances amyloid formation in human pancreatic islet culture, leading to cell death; however, treatment with heparinase III significantly reduces amyloid deposition and cell death [120]. The sulfate content and specific carbohydrate backbone of perlecan, an HSPG that is a significant component of all vascularized basement membranes, also enhances hIAPP fibrillation in a dose-dependent manner [121].

Different isoforms of apolipoprotein E (i.e., ApoE2, ApoE3, and ApoE4) have been explored for their anti-aggregation capacity. All ApoE isoforms reportedly inhibit hIAPP aggregation at high stoichiometric ratios. During hIAPP aggregation, ApoE interferes with nucleation and elongation, thus preventing fibrillation. It, however, exerts no effects on preformed fibrils. ApoE also protects pericytes from the toxic effects of hIAPP [122].

3.8. Glycation of hIAPP

Advanced glycation end products contribute significantly to T2DM progression [123]. The glycation of hIAPP by glyoxal changes its conformation from the random coil to β-sheet, promotes the formation of high-molecular-weight oligomers and amyloid aggregates, and exerts cytotoxicity in mouse insulinoma 6 (MIN6) cells [124,125]. Cross-linked insulin molecules alleviate hIAPP aggregation and associated cytotoxicity, whereas glycated insulin enhances hIAPP-induced cytotoxicity in vitro [126]. This explains the possible association among chronic hyperglycemia, insulin, hIAPP, and T2DM. A study using pancreatic tissue from patients with T2DM and hIAPP-transgenic hemizygous mice has demonstrated that increased RAGE expression is associated with hIAPP-induced cytotoxicity. RAGE binds only to the toxic form of hIAPP that mediates the dysfunction and apoptosis of β-cells. The inhibition of RAGE activity by deleting the RAGE gene (*Ager*), blocking with antibodies, or treating with soluble extracellular ligand-binding domains shows a protective effect against RAGE-mediated hIAPP cytotoxicity [127].

4. Current therapeutic interventions available for T2DM management

Most drugs, oral and/or injectable, prescribed for managing T2DM, depend on an individual's condition and are centered on balancing blood sugar levels. In addition, lifestyle changes,

physical activity, and dietary habits are also recommended to manage symptoms and prevent other complications. The commonly used therapeutic interventions, for example, biguanides such as metformin, suppress glucose production in the liver, whereas thiazolidinediones such as rosiglitazone enhance peripheral insulin sensitivity. Other drugs used to manage T2DM include sulfonylureas such as glyburide, dipeptidyl peptidase-4 inhibitors such as sitagliptin, and meglitinides such as repaglinide boost insulin secretion from the already stressed β-cells. Some medications follow different routes: α-glucosidase inhibitors reduce the carbohydrate degradation rate, glucagon-like peptide-1 mimetics such as exenatide suppress glucagon secretion from the pancreas, and dapagliflozin induces sodium-glucose cotransporter 2 inhibition [128–130]. In severe cases where oral medications are not adequate for T2DM treatment, injectables are prescribed. Exogenous insulin is an excellent alternative to achieving reasonable metabolic control. Commercially available insulin can be classified according to its source (human, bovine, porcine, or synthetic) and the duration of its action (i.e., short, intermediate, or long) [128,131]. Although the use of these drugs keeps T2DM under control, they also have certain limitations in terms of their efficacy, cost, tracking dosage, mild (e.g., anorexia, nausea, abdominal discomfort, diarrhea, and urogenital tract infections) to severe adverse effects (e.g., weight gain and cardiac arrest/heart failure) [128,132], and activity loss over prolonged usage. In severe cases, islets or whole pancreas transplantation can be performed; however, the costs associated with this surgery constitute the primary disadvantage of transplantation and make it an unusable alternative for the general public [133]. Although the side effects are more or less dependent on an individual's physical state, they need to be critically assessed for each patient. Despite the fact that multiple drugs are available for T2DM management, several patients with T2DM fail to achieve normal glycemic levels and are at risk of developing other complexities. Considering the multiple factors responsible for T2DM development, it is indeed a challenge to find novel drugs/pharmacological targets for a more efficient management of T2DM.

5. hIAPP as a drug target

As mentioned earlier, hIAPP plays a significant role in disrupting the physiology of pancreatic β-cells under diabetic conditions. Thus, it acts as a key target for T2DM management. The formation of hIAPP aggregates occurs much earlier than the development of acute hyperglycemia in patients with T2DM [11]. Amyloid deposition in the islets is a major factor responsible for islet transplant failure [134,135]. Notably, amyloid fibers are extremely strong, stable, and difficult to disaggregate. Thus, the search for inhibitors of hIAPP aggregation is an active area of research. Several inhibitors that have been identified not only inhibit hIAPP aggregation but also disassemble the preformed fibrils. However, most of these studies have been conducted on synthetic peptides using rodents and rodent-derived cell lines. The following subsections detail the different agents that have been developed as the potential inhibitors of hIAPP aggregation (Fig. 3). In addition, the effects of known drugs on hIAPP aggregates have been discussed.

5.1. Known antidiabetic molecules and repurposed drugs

Several known antidiabetic molecules and other drugs have been evaluated for their anti-amyloidogenic potential. Table S1 [136–142] summarizes the results obtained by studies on drugs such as rifampicin, sitagliptin, metformin, and nonsteroidal anti-

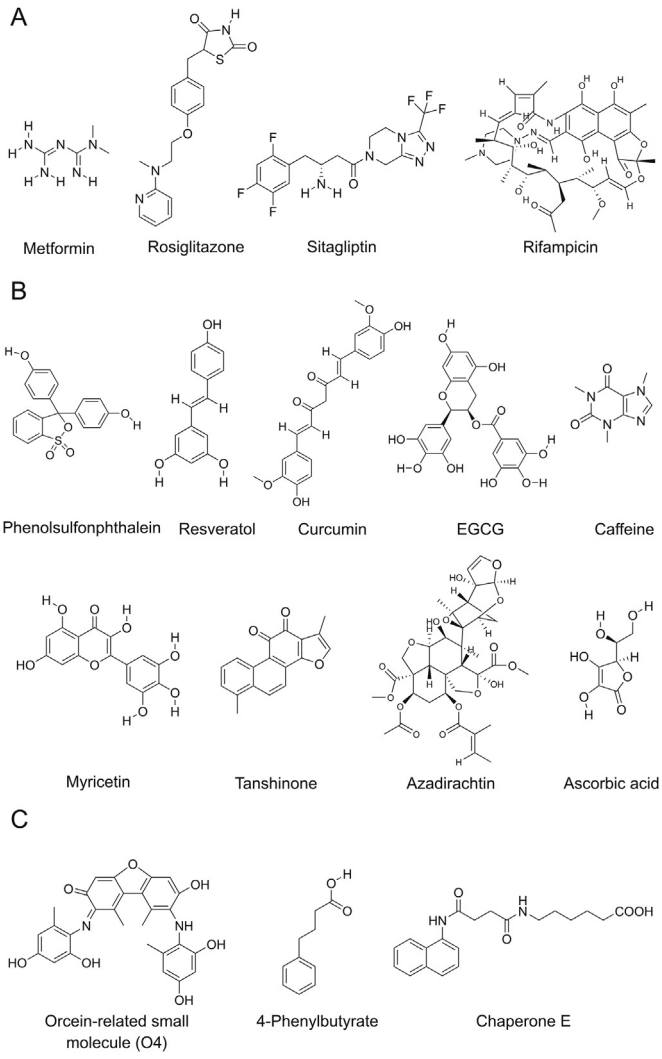

Fig. 3. Inhibitors of hIAPP aggregation. Representative structures of (A) known antidiabetic compounds, (B) small organic molecules, and (C) chaperones.

inflammatory drugs. Metformin, the most effective and commonly used drug till date for T2DM management [143], promotes the formation of the amyloid peptide associated with Alzheimer's disease [144,145]. However, in hIAPP-transgenic mice, metformin treatment has been reported to significantly reduce the prevalence and severity of amyloid formation in the islets [137]. Combination therapy with these drugs has also been attempted. The combination of metformin and sitagliptin shows synergistic effects in preserving the mass and function of β-cells and also enhancing insulin sensitivity. However, this therapy has been associated with hemorrhagic pancreatitis, increased ductal turnover, and metaplasia in hIAPP-transgenic rats [138]. Owing to the associated side effects, these drugs have not been promoted as hIAPP inhibitors for T2DM management [136,138]. Recently, the antimalarial drug artemisinin has shown to disaggregate hIAPP fibrils into monomers by disrupting hydrophobic interactions and hydrogen bonding [140]. Along these lines, tetracycline derivatives, namely, minocycline hydrochloride, methacycline hydrochloride, and doxycycline, have shown potential as the inhibitors of hIAPP aggregation and could also disintegrate the preformed fibrils [141].

5.2. Insulin and insulin-degrading enzyme

Atomistic discrete molecular dynamic simulations performed to determine the correlation between insulin and hIAPP show that the inhibition of hIAPP aggregation by insulin is determined by insulin oligomers and high Zn^{2+} concentrations are crucial for maintaining their oligomeric state [146]. Insulin acts as a kinetic inhibitor and not as a thermodynamic inhibitor of hIAPP aggregation [147]. Moreover, it shows a dual effect on hIAPP aggregation. Initially, insulin-hIAPP complexes restrict the early phase of hIAPP aggregation, but with increasing incubation period, they serve as a seed for further aggregation. This suggests that insulin acts as an inhibitor of hIAPP aggregation in healthy individuals, whereas it promotes hIAPP aggregation in patients with T2DM [147]. Biophysical analysis performed with hIAPP analogs (H18R-IAPP, H18K-IAPP, H18A-IAPP, and H18E-IAPP) has suggested an important role of His18 in hIAPP interactions. Insulin decreases hIAPP fibrillation in solution and in presence of the membrane wherein the interactions are mediated by His18 [148].

Insulin-degrading enzyme (IDE), also called insulysin, is a Zn^{2+}-binding metalloendopeptidase that degrades insulin and hIAPP and thus plays an important role in preventing hIAPP amyloid formation [149]. IDE locus has been recognized as one of the risk loci for T2DM [150,151]. The inhibition of IDE by the antibiotic bacitracin induces the formation of hIAPP amyloids and eventually leads to increased hIAPP-induced cytotoxicity in RIN-m5F cells [152]. Another Zn^{2+}-binding metalloendopeptidase, neprilysin (NEP), present on the surface of pancreatic β-cells, degrades hIAPP and inhibits their aggregation [153,154]. Transgenic mice overexpressing hIAPP exhibit elevated levels of NEP when compared with their wild-type counterparts; this elevation might be to tackle the accumulation of extracellular hIAPP species in these mice [155]. NEP degrades hIAPP and prevents apoptosis by an unknown mechanism in rat INS 832/13 cells [154].

5.3. hIAPP mimetics and peptides

The *N*-methylated full-length hIAPP mimic [(N−Me)G24, (N−Me)I26]-IAPP (IAPP-GI) is an hIAPP receptor agonist. At the physiological pH, the solubility of IAPP-GI is high and it is non-amyloidogenic and noncytotoxic; in this condition, IAPP-GI not only inhibits hIAPP misfolding into β-sheets, fibrillogenesis, and cytotoxicity at nanomolar concentrations but also disaggregates the preformed fibrils. When the mixture of hIAPP and IAPP-GI peptides was added to RIN-5fm cells, a significant increase was noted in cell viability [156]. Pramlintide, another hIAPP analog, is a chimeric peptide comprising the primary sequence of human amylin with three proline substitutions at positions Ala25, Ser28, and Ser29 (derived from the rat amylin sequence). It retains all beneficial properties of the native amylin but does not form aggregates [157]. The only major disadvantage with pramlintide administration is that patients receiving pramlintide and insulin require two separate injections before meals because insulin is solubilized at a neutral pH, whereas pramlintide is solubilized at an acidic pH of 4 [158]. A comparative in vitro study of rat IAPP, pramlintide, and two mutants of pramlintide, H18R PM and F23L PM, has revealed that pramlintide is a better inhibitor owing to its higher sequence similarity with hIAPP than rat IAPP and other mutants and this effect is dose-dependent [159]. Another analog of human amylin, davalintide, comprises 32-amino acids and shows similar activities as amylin but for a longer duration (as its release from the receptor is slower than that of amylin) [160]. It has been effectively used in rats for treating obesity. However, during the second phase of clinical trials, davalintide showed no better effects than pramlintide; hence, the development of the former drug was discontinued [161]. Table S2 [156,159,162–198] presents some other peptide inhibitors designed and evaluated for their potential against hIAPP aggregation, for example, inhibitors derived from an internal sequence of hIAPP; those containing natural amino acids [162,169], D-amino acids [170], or non-natural amino acids [175,182]; and *N*-alkylated [186], cyclic [189,190], and conjugated [188] peptide inhibitors. In 2009, Potter et al. [169] identified the hexapeptide ANFLVH (residues 13–18) as a potent inhibitor of hIAPP aggregation in vitro and demonstrated that this peptide can significantly increase the viability of human islets in culture. The same inhibitor was used in a study where hIAPP-transgenic mice were fed with a high-fat diet and were administered with ANFLVH (50 μg/kg) prepared in saline for 6 months; the results showed the inhibition of hIAPP aggregation. The peptide possibly functions by disrupting peptide-peptide interactions and thus prevents fibrillation. As a result, a significant decrease in amyloid deposition and an increase in β-cells' survival rate were observed. A significant increase in glucose-stimulated insulin secretion (GSIS) and glucose homeostasis was also observed in these mice at the end of the study; however, no changes in the fasting plasma insulin level and IR index were noted [170].

When coincubated with the entire peptide, internal hIAPP fragments, SNNFGA (residues 20–25) and GAILSST (residues 24–29), inhibit β-sheet formation and hIAPP aggregation in vitro. In addition, the SNNFGA fragment mitigates the cytotoxic effects of hIAPP in RIN-1056 cells [162]. Similarly, the monomers and oligomers of the NFGAILSS (residues 22–29) fragment also inhibit hIAPP aggregation by restricting the β-strand conformation. The NFGAILSS oligomers possibly interact with the connecting loop (the same residues as those of NFGAILSS) of two β-strands, forming different secondary structures [183]. A synthetic pentapeptide, Phe-Leu-Pro-Asn-Phe (FLPNF), inhibits hIAPP fibrillation by binding to the hIAPP monomer. Molecular docking has identified the binding site between FLPNF and hIAPP and predicted that the cation-π and π−π stacking interactions among them prevent fibrillation [193]. Furthermore, this pentapeptide protects hIAPP-expressing INS-1 cells from hIAPP-induced apoptosis by inhibiting the mTOR pathway and augmenting autophagy [194]. These peptide fragments impede the conformational change of hIAPP, maintaining its monomeric form, thereby preventing fibrillation. The insulin-derived peptide EALYLV loaded onto polyethyelene glycol (PEG)-modified nano-sized graphene oxide (nGO@PEG@E) inhibits hIAPP aggregation via electrostatic adsorption and specific binding to the active sites of hIAPP. The treatment of INS-1E cells with hIAPPs and nGO@PEG@E shows a significant decrease in the level of intracellular ROS and normalization of mitochondrial membrane potential, thus increasing cell viability [179]. *N*-methylated peptides (H_2N-RGAmNFmLVmHGR-$CONH_2$ and H_2N-RGANmFLmVHmR-$CONH_2$) derived from the binding region (residues 11–20) of hIAPP also show dose-dependent inhibition of hIAPP aggregation. Moreover, these peptides protect the human pancreatic 1.4E7 cell line against hIAPP-mediated cytotoxicity through an unknown mechanism [186]. β-sheet breaker hybrid peptidomimetics (BSBHps) formed by the insertion of different isomers of aminobenzoic acid in an hIAPP fragment (22–27) have also been evaluated for their anti-aggregation potential. Likewise, BSBHps containing the ortho (2-Abz) and meta (3-Abz) isomers have been identified as the potent inhibitors of hIAPP aggregation in vitro [198].

5.4. Small organic molecules and natural products

Several natural products and small molecules present abundantly in certain foods and plant materials have been

substantially used in the past to manage T2DM [199]. Among these, natural products belonging to the flavonoid and curcuminoid families have been extensively assessed for their potential as hIAPP aggregation inhibitors (Table S3) [200–231]. As mentioned earlier, most of these studies have been conducted using cell lines derived from pancreatic insulinoma of mouse or rat origin. For example, epigallocatechin gallate (EGCG), a flavonoid from green tea, is one of the most studied compounds for its anti-aggregation activity against hIAPP [232]. Biophysical analysis has shown that the binding of EGCG to hIAPP monomers alters their conformation to prevent aggregate formation. EGCG acts in a dose-dependent manner, and hydrophobic interactions are important for its action [207,208]. Recently, Franko et al. [209] conducted a comparative study using hIAPP-transgenic homozygous, hemizygous, and wild-type control mice and found that the hemizygous mice showed normal physiology (i.e., normal plasma glucose, insulin, lipid, alanine transaminase (ALT), and aspartate aminotransferase (AST) levels), but had amyloid aggregates in their insulin-secretory vesicles. The homozygous transgenic mice showed increased levels of ALT and AST, but decreased levels of insulin with dyslipidemia and the presence of hIAPP amyloid aggregates, which destroyed the islet anatomy and promoted T2DM development. The treatment of these mice with EGCG for 3 weeks decreased hIAPP aggregation and correlated with increases in the islet number and area in case of the hemizygous mice. The untreated homozygous transgenic mice showed decreases in the islet number and area [209]. In vitro and in silico analyses of hIAPP-EGCG binding suggest that their interaction occurs through multiple mechanisms involving π–π stacking, van der Waals, alkyl, π-alkyl, hydrogen, and carbon-hydrogen interactions. The hIAPP amino acid residues R11, L12, S19, A25, I26, L27, and Y37 are important for EGCG binding. After binding, EGCG reduces the intra- and inter-molecular interactions involved in the formation of the β-sheet structure [209]. Furthermore, EGCG depolymerizes preformed aggregates to a more amorphous structure that is nontoxic. Zn^{2+} reportedly enhances the anti-amyloidogenic potential of EGCG [233].

Azadirachtin, a limonoid isolated from Neem (*Azadirachta indica*), has been shown to inhibit hIAPP amyloid formation and disaggregate preformed fibrils. Azadirachtin supplementation corrects the functional defect in hIAPP-exposed mouse pancreatic islets by enhancing GSIS [224]. Another small organic molecule called myricetin, which is commonly derived from vegetables, fruits, nuts, berries, tea, and red wine, prevents hIAPP fibrillation and disaggregates preformed fibrils, thus inhibiting cytotoxicity in INS-1E cells. It reduces oxidative stress and the associated DNA and membrane damages and restores the mitochondrial membrane potential. Myricetin supplementation also restores the function of pancreatic islets exposed to hIAPP [206].

5.5. Nanoparticles, nanobodies, and quantum dots

The OH-terminated polyamidoamine dendrimer, a polymeric nanoparticle, has shown potential as an inhibitor of hIAPP aggregation and cytotoxicity in MIN6 cells, insulinoma cells derived from NOD/Lt mice (NIT-1 cells), and mouse pancreatic islets [234]. Binding of hIAPP with this dendrimer results in decreased interpeptide contacts and hydrogen bonds, which prevents the self-association of the peptides and their aggregation [234]. Another unique approach has been developed in which an hIAPP fragment (residues 22–31) has been combined with the PDB-3B9V human antibody to generate a nanobody called M1. This was followed by the incubation with gold nanoparticles to produce M1-gold nanoparticle conjugates. These conjugates are effective as the inhibitors of hIAPP aggregation [235]. The carbon nanoparticles fullereno [236] and fluorinated graphene quantum dots [237] have been shown to interfere with hIAPP fibrillation and inhibit amyloid formation. Likewise, nanoparticles conjugated with iron oxide and silver have also been assessed for their anti-amyloidogenic potential; only silver-conjugated nanoparticles have shown inhibitory effects on hIAPP aggregation [238]. Table S4 [234–242] summarizes the results of studies using nanoparticles, nanobodies, and quantum dots. A recent study has demonstrated the use of mesoscopic chiral left- and right-handed silica nanoribbons (L/R–SiO_2) to accelerate hIAPP aggregation toward fibrillation; these fibrils are associated with reduced cytotoxicity in pancreatic β-cells and zebrafish embryos [58].

5.6. Metals and metal complexes

Studies using electrospray ionization-MS with Zn^{2+} have shown that a single ion binds to hIAPP and inhibits dimer formation. However, when used in high concentration, Zn^{2+} promotes hIAPP oligomerization while forming an energetic barrier for the formation of amyloid fibers [243,244]. Similar findings were obtained in a NMR study conducted to determine the role of Zn^{2+} in hIAPP aggregation. At an acidic pH, Zn^{2+} was shown to bind at the His18 residue and disturb the secondary structure mainly through an electrostatic effect [245]. A study using electron paramagnetic resonance and NMR spectroscopy to explore the interaction between Cu^{2+} and hIAPP fragments has revealed that at the physiological pH, Cu^{2+} binds with hIAPP at the His18 residue and subsequent/upcoming amide groups toward the C-terminal, thereby inhibiting β-sheet formation and fibrillation [246]. Using thioflavin T fluorescence assays and transmission electron microscopic analysis of INS-1E cells, a previous study has shown that gold-sulfur complexes such as dichloro-diethyl-dithiocarbamate and dichloro-pyrrolidine-dithiocarbamate gold complexes inhibit hIAPP fibrillation in vitro [247]. Likewise, heme [248], methionine-ruthenium complex [249], and platinum-ruthenium complex [250] exert a strong inhibitory effect on hIAPP aggregation. All these agents have shown their inhibitory activity in vitro, and it would be interesting to explore their effects in vivo in the future (Table S5) [243–252].

5.7. Chaperones

Using biophysical techniques such as attenuated total reflectance Fourier-transform infrared spectroscopy, atomic force microscopy, and circular dichroism spectroscopy, chaperones inhibiting hIAPP aggregation have been identified (Table S6) [253–255]. The pharmacological chaperone orcein-related small molecule (O4) has been shown to stabilize hIAPP when added to monomeric hIAPP, thus increasing the viability of INS-1E cells [253]. O4 does not affect the original hIAPP aggregation pathway; however, it promotes the stabilization of nonfibrillar and globular assemblies of hIAPP in a dose-dependent manner. Therefore, O4 has been identified as a thermodynamic inhibitor of hIAPP aggregation. O4 disassembles preformed hIAPP aggregates into smaller species [253].

The chemical chaperone proline shows the same effect on hIAPP aggregation as O4 but is less efficient. A potential protein chaperone, serum amyloid P (SAP) component, leads to the formation of hIAPP/SAP aggregates when coincubated with hIAPP in equimolar concentrations, thus preventing hIAPP aggregation [253]. Oral administration of the chemical chaperon 4-PBA to hIAPP-transgenic mice reverses hIAPP amyloid aggregation, consequently reducing amyloid deposition and restoring GSIS in these mice. PBA also impedes changes in the expression of genes

involved in inflammation in the pancreatic islets derived from hIAPP-transgenic mice. Under glucolipitoxic conditions, PBA ameliorates the defects in insulin secretion and restores cell viability. In silico studies have shown that PBA binds with hIAPP monomers and oligomers and prevents fibrillation [254].

Results from in silico, in vitro biophysical and biochemical studies have been combined to introduce naphthalene-based pharmacological chaperones, namely, chaperone A (*N*-(2-aminoethyl)-N0-1-naphthylsuccinamide), chaperone B (methyl (2-{[4-(1-naphthylamino)-4-oxobutanoyl]amino}ethyl)dithiocarbamate), chaperone C ((2*R*)-2-(6-methoxy-2-naphthyl) propanoic acid (Naproxen)), chaperone D (*N*-[4-(1-naphthylamino)-4-oxobutanoyl]-β-alanine), chaperone E (6-{[4-(1-naphthylamino)-4-oxobutanoyl]amino} hexanoic acid), and chaperone F (N3,N30-ethane-1,2-dyilbis (N1-1-naphthylsuccinamide). These chaperones bind to hIAPP like stearic zipper zone and retard the aggregation process. Out of these, chaperone E is the most effective inhibitor that improves the viability of cerebellar granule cells exposed to hIAPP [255].

6. Conclusions

hIAPP plays a pivotal role in important physiological processes, including glucose homeostasis maintenance, feeding, and satiety. The misfolding of hIAPP and formation of oligomeric species and amyloidogenic aggregates represent key events in the pathophysiology of T2DM that leads to the death and dysfunction of pancreatic β-cells. Therefore, targeting the hIAPP aggregation pathway can be considered as a promising strategy for the management and/or possible reversal of T2DM. As discussed in this review, various inhibitors have been designed that target different toxic intermediates of the hIAPP aggregation pathway and convert them into nontoxic species or alter the aggregation kinetics of the pathway. Furthermore, several other molecules have shown the potential to disaggregate the hIAPP fibrils into nontoxic intermediates. Among the various compounds assessed for their anti-hIAPP-aggregation potential, EGCG has entered clinical trials. On the basis of these findings, more comprehensive and elaborate in vivo and in vitro studies are warranted in the future to improve our understanding and develop drugs targeting hIAPP aggregation. In the future, these drugs can be repurposed for targeting other protein-misfolding disorders because of the common mechanism underlying these pathologies.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2022.04.001.

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