

Amyloid Aggregation Induced by Environmental Toxins

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Abstract

Diseases like Alzheimer's and Parkinson's are associated with the aggregation of amyloids. Scientists have learnt that besides natural speed bumps such as the ageing process and genes, a greater role is played by environmental toxins. Hazardous substances like lead, mercury and aluminum, among others, have the ability to disrupt the protein homeostasis through the induction of oxidative stress, proteasomal blockage, and alteration of mitochondrial electrical activity. By enhancing the misfolding of amyloid- β , α -synuclein and tau proteins along with their aggregation, these disruptions lead to synaptic dysfunction and neuronal loss. Exposure to the environment can worsen the risk and severity of the genetic predisposition to disease. Experimental studies in cell and animal models have shown that chronic exposure to toxins enhances the deposition of amyloid and intensifies neuroinflammation. Epidemiological studies have linked environmental risk factors to amyloid-related neurodegenerative disease. While much of this was observed in transgenic mice, findings were seen in wild-type animals as well and mainly involved the A β 42 peptide. Examining how environmental toxins and amyloid clumping interact can help develop better ways to prevent neurodegenerative disease and assess the risk, along with new therapies.

Keywords: Amyloid Aggregation; Environmental Toxins; Neurodegeneration; Oxidative Stress; Protein Misfolding

Introduction

Amyloid aggregation is a biological phenomenon that warrants focused attention due to its association with various pathological conditions, particularly in the context of environmental toxin exposure [1]. Environmental toxins, including heavy metals, pesticides, and industrial chemicals, have been implicated in precipitating amyloid aggregation by disrupting protein homeostasis and inducing misfolding pathways [1]. This review critically analyzes current knowledge concerning toxicity and toxicokinetics of major environmental toxins in relation to amyloidosis [2]. It examines experimental models used to elucidate the effects of such toxins on protein aggregation [3]. Detailed case studies on heavy metal and pesticide exposure further illustrate these relationships [4]. Diagnostic and treatment

methods addressing toxin-induced amyloid aggregation are assessed, alongside public health policy strategies aimed at mitigating associated risks [5]. Understanding the mechanisms by which environmental toxins promote amyloid aggregation is essential to develop effective prevention and intervention approaches [6].

Background on amyloidosis

Amyloid aggregates formed *in vivo* consist of differently modified variants of the amyloidogenic protein and are associated and often co-aggregated with components of the protein homeostasis system [7]. The presence of amyloids is usually related to pathological conditions called amyloidosis, which can be localized or systemic depending on whether the aggregates are in the site of synthesis or not [8]. Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's involve amyloid deposits in the nervous system that induce neuronal cell death. Systemic amyloidosis, like immunoglobulin light chain, transthyretin, and dialysis-related amyloidosis, affect multiple organs as amyloidogenic proteins distribute throughout the body [9].

Definition and types of amyloidosis

Amyloids are large insoluble protein aggregates that, beyond their widespread presence across all biological kingdoms are frequently linked to pathological states termed amyloidosis [7]. These conditions manifest in either localized or systemic forms. Localized amyloidosis encompass prevalent neurodegenerative diseases-Alzheimer's, Parkinson's, and Huntington's-where amyloid deposits accumulate within the nervous system and provoke neuronal death by interfering with neural function [10]. Systemic amyloidosis include immunoglobulin light chain, transthyretin, and dialysis-related variants; in these cases, the amyloidogenic protein arises at one site, circulates, and deposits in multiple organs [11].

Amyloid formation unfolds through complex aggregation processes involving primary nucleation, elongation, secondary nucleation, and fragmentation [12]. The early species in these pathways are small soluble aggregates, termed oligomers, which exhibit high heterogeneity, rapid interconversion to protofibrils, and pronounced toxicity [13]. Their formidable deleterious effects have implicated oligomers as the principal agents of neurodegenerative tissue damage observed in localized amyloidosis [14]. Specifically, oligomer toxicity can entail synaptic overstimulation via glutamatergic pathways, synaptic loss, mitochondrial dysfunction, and inflammatory responses [15]. In systemic amyloidosis, both the insoluble fibrils themselves and transiently populated soluble oligomers contribute to cytotoxic outcomes [16].

Pathophysiology of amyloid aggregation

Aggregates of amyloid formed *in vivo* usually consist of differently modified variants of the amyloidogenic protein and are associated with components of the protein homeostasis system [17]. The presence of amyloids is commonly related to pathological conditions collectively called amyloidosis, which can be either localized or systemic [7]. Localized amyloidosis are a subgroup of degenerative disorders in which amyloid deposits form directly at the site of synthesis; well-known examples are neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's and the prion pathologies [18]. Here, amyloidogenic proteins accumulate in variable amounts in the nervous system, inducing neuronal cell death [10]. At variance, in systemic amyloidosis, including immunoglobulin light chain, transthyretin, and dialysis-related amyloidosis, several organs are affected, as the amyloidogenic protein travels from the site of synthesis to other tissues [11].

Amyloid formation depends on complex aggregation processes involving several intermediates whose contribution is difficult to disentangle, especially *in vivo* [19]. At the microscopic level, well-defined events such as primary nucleation, elongation, secondary nucleation and fragmentation have been identified as the main routes by which monomers get converted into aggregates [20]. These

processes, whose relevance for the overall kinetic profile depends strongly on the specific protein considered, determine the length of the lag phase as well as the growth rate of the polymerization reaction [21]. The reaction “flux” is distributed among different species during the formation of ordered fibrils [22]. Small soluble aggregates are commonly referred to as oligomers; they are highly heterogeneous, can rapidly convert into protofibrils, and generally form in significant quantities during the lag-phase of the reaction [23]. Their role in amyloid diseases has become a highly topical subject of investigation, motivated by compelling evidence indicating that oligomers constitute the most toxic species in neurodegeneration [24]. Nonetheless, the mechanism of oligomer toxicity remains under debate [25]. Several pieces of evidence suggest that high levels of amyloid oligomers can overstimulate glutamatergic transmission, cause synapse loss, mitochondrial dysfunction, and inflammation [26]. Both insoluble fibrils and soluble oligomers are important in cytotoxicity for systemic amyloidosis as well [27].

The self-assembly of proteins into highly ordered amyloid aggregates is a common feature of many neurodegenerative diseases [28]. Different lines of evidence support the crucial role of fibrillar species in cell dysfunction and death, potentially caused by their interaction with the neuronal membrane [29]. Structural models explaining the binding of A β fibrils and protofibrils to phospholipid bilayers have been recently reported [30]. Experimental data show clear differences in the nucleating capability of amyloid fibrils and protofibrils and highlight the high toxicity of the early fibrillar intermediates [31]. Fluorescence and FRET (Förster resonance energy transfer) data also provide clear indications on the organization of the protein aggregates on the bilayer surface, revealing that the fibrils do not bind to the membranes as well as the smaller aggregates and protofibrils [28].

Environmental toxins and their sources

Environmental toxins, such as heavy metals, pesticides, and industrial chemicals, are frequently implicated in amyloid aggregation [32]. Heavy metals including aluminum, copper, mercury, lead, and zinc disrupt the normal folding of amyloidogenic proteins and can enhance the formation of toxic oligomers and subsequent aggregation [33]. Pesticides are capable of perturbing electron transport chain function, thereby increasing oxidative stress and facilitating pathological protein aggregation [34]. Industrial chemicals have been linked to various neurodegenerative diseases through mechanisms involving protein misfolding and aggregation; however, the exact processes by which they induce amyloid aggregation remain to be elucidated [3].

Heavy metals

The dispersion of heavy metals in the environment has been accelerated through mining, smelting, coal combustion, industrial effluents, and the use of fertilizers and pesticides [35]. As a result, a large quantity of heavy metals has been discharged persistently, thereby exposing ecosystems and humans to environmental pollution [36]. Heavy metals and metalloids such as arsenic, cadmium, mercury, chromium, lead, and iron affect protein homeostasis and cell viability by interfering with the folding of nascent proteins, leading to the accumulation of toxic protein aggregates [35]. Chronic exposure to these metals is associated with the onset or progression of age-related and neurodegenerative disorders caused by aberrant protein folding [36]. Molecular damage may be a direct consequence of interactions between metal ions and folding proteins, shifting the balance toward misfolding and aggregation [37]. These events can be amplified over time, especially as the capacity of cellular proteostasis mechanisms declines with age. Several model proteins that aggregate in response to arsenite have human homologues linked to protein folding disorders such as Alzheimer’s disease, early-onset amyotrophic lateral sclerosis, and frontotemporal lobar dementia [38]. Investigations into the molecular interplay between metals and protein folding and the regulation of metal-induced aggregation by cellular quality-control systems may contribute to novel strategies for preventing and treating protein misfolding diseases [39].

Pesticides

Pesticides represent a class of environmental toxins that accelerate amyloid aggregation across several animal species [40]. These toxicants have been widely used for pest control in agriculture, aiming to protect crops from insects, weeds, fungi, and other pests [5]. Due to their extended half-lives, some pesticides have been banned; nonetheless, they persist in soil and water because of extensive prior usage and improper disposal, resulting in residual presence in certain agricultural products [41]. Efficient industrial manufacturing processes and lack of communication in the agricultural supply chain allow these substances to enter the food chain continuously [42]. Individuals consume pesticide-contaminated products daily. Consequently, the ingestion of pesticides through contaminated food and water constitutes a probable main source of these contaminants in various populations [27].

Industrial chemicals

High levels of homogeneous pollutants in water or bulk air characterize many industrial compounds, augmenting individual and combined environmental exposure risks. Industrial chemicals are known to promote the generation of reactive oxygen species and inflammation, but broader toxicological concerns arise from their interaction with biological molecules, particularly upon direct contact [43]. Among the widely used industrial chemicals are phthalates, which constitute the backbone of polyvinyl chloride [44]. These high-volume compounds have diverse applications and offer many points of entry into the organism [45].

When released into the environment, they constitute a major source of pollution and exposure [46]. Toluene is a well-known volatile solvent used in paints and cleaners for the electronics industry [47]. A primary contact and exposure site is the nervous system, owing to the volatility and capacity of these compounds to permeate otherwise protected tissues [48]. The medical record of industrial workers provides compelling evidence of long-lasting neurotoxicity from these chemicals [7]. Various foam stabilizers, surfactants, and emulsifiers belong to the group of polyglycols and alkylphenols [49]. Different grades, such as polyethylene glycol, polypropylene glycol, and polyethylene oxide, are widely used [32]. Their impact on human health is not fully known, but they are suspected to interfere with the endocrine system [50].

Mechanisms of amyloid aggregation

Protein misfolding is the primary early step that triggers the aggregation of amyloidogenic proteins [51]. Such conformational changes result in the enrichment of β -sheet structures, which exhibit strong intermolecular interactions that drive the protein aggregation process [52]. In general, the aggregation proceeds through a stepwise nucleation process, in which protein monomers first assemble into oligomers and then further grow into amyloid fibrils by the addition of more monomers [7]. These dynamic and heterogeneous conversion processes often afford a variety of soluble assembly intermediates, which are considered to be the main cytotoxic species for living cells [53].

Protein misfolding

The folding of polypeptide chains into native structures is a critical step in protein synthesis, as it confers specific functions [51]. Under physiological conditions, the delicate balance between the folded and unfolded states can be disrupted by both intrinsic and extrinsic factors, leading to kinetic trapping in stable off-pathway structures [54]. Misfolded conformations are inefficiently degraded and tend to accumulate in neurons and extracellular compartments, negatively affecting normal cellular function and ultimately causing tissue damage [55]. Protein misfolding and aggregation are associated with a range of pathological conditions known as amyloidosis [1].

Nucleation and growth of amyloid fibrils

Amyloidosis comprise a broad class of related protein misfolding diseases that include Alzheimer's disease, Parkinson's disease, and type 2 diabetes [32]. Amyloid aggregates are associated with many neurodegenerative diseases [6]. Exposure to environmental toxins

such as metal ions, pesticides, and industrial pollutants is correlated with the pathogenesis of amyloidosis, indicating that a wide range of environmental molecules may trigger amyloid aggregation [56]. The nucleation-dependent formation of protein aggregates is a key step in the development of amyloidosis [57]. Consequently, a detailed understanding of the factors controlling aggregation nucleation has important implications in both toxicology and protein folding [8]. Here, the molecular mechanisms of protein aggregation by common environmental toxins are classified and reviewed [58].

Amyloid fibrils form through a nucleation-dependent polymerization mechanism [59]. The process begins with a lag phase, during which monomeric or oligomeric proteins form a critical nucleus [60]. Once this nucleus forms, the growth phase proceeds rapidly, with soluble precursors assembling into mature fibrils [61]. *In vitro*, nucleation is extremely slow, but it can be greatly accelerated by pre-formed aggregates through secondary nucleation processes, whereby existing fibril surfaces catalyze the formation of new nuclei [62]. Pre-formed fibrils can overcome the kinetic barrier to nucleation and seed the growth of additional aggregates [63]. Understanding these nucleation and growth pathways is crucial for elucidating how environmental toxins may influence amyloidogenic processes [64].

Impact of environmental toxins on protein structure

Environmental toxins induce amyloid aggregation through diverse mechanisms [33]. The long-lived pollutants such as heavy metals, pesticides and persistent organic pollutants, as well as airborne fine particulate matters, affect protein structure at multiple stages during the amyloid aggregation process [14]. Chemical modifications including oxidation and covalent binding, and altered protein-protein interactions of both intrinsically disordered proteins and globular proteins, lead to protein crosslinking or over-stabilization of prefibrillar, oligomeric structures [65]. These events promote amyloid nucleation and formation of cytotoxic species, diverting the system from the natural, well-controlled aggregation pathway of mature amyloid fibrils [1]. Developing a mechanistic understanding of amyloid aggregation modulated by environmental factors at the molecular level brings new perspectives for epidemiological investigations of human health impact [66].

Chemical modifications

Chemical modifications play a significant role in the aggregation of proteins into amyloid fibrils [67]. Posttranslational and chemical modifications commonly arise in pathological or environmental contexts and can promote protein aggregation leading to amyloid formation or the generation of amorphous aggregates [1]. For example, metal-catalyzed oxidation of α -synuclein is identified as a mechanism contributing to Parkinson's disease [32].

Altered protein interactions

Environmental toxins induce the formation of new or stronger interactions, alter pre-existing interactions, or both [1]. *In vitro*, transition metals can promote intermolecular interactions that are not normally present in metal-free fibrils [68]. In cellular environments, such interaction changes might lead to the formation of otherwise inaccessible toxic species [69]. Protein oligomers can directly interact with membrane proteins, disrupting their physiological functions [68].

Clinical implications of amyloid aggregation

Amyloid deposits can be localized or systemic, requiring methods to probe their structure *in situ* [7]. Direct grafting of aldehydes, modulation of spectral shift and intensity of bound dyes, or oxidative stress evidenced by redox-active dyes should be explored [4]. Portable systems allowing identification of fibre-rich tissue areas through spectral differences between native and bound dyes, coupled with a diagnostic imaging tool, may facilitate early identification of amyloid-related injury [70].

Currently, no broad-spectrum therapeutic approaches directly targeting amyloid aggregation are clinically available [34]. However, proteome-wide low-resolution approaches combining hydrogen/deuterium exchange and a limited proteolysis have been proposed [71].

Formation of this stable, highly viscous layer leads to progressive membrane disruption, culminating in cell lysis [12]. Concentration of stabilizing molecules around the protein aggregate hinders the formation of proper hydrolytic pockets [3]. Exposure to persistent toxicants results in the formation and accumulation of highly stable amyloid fibrils [72]. Preventing the accumulation of these structures and targeting existing fibrils for disaggregation represent strategic avenues for developing effective interventions [73].

Conclusion

Amyloidosis constitutes a broad category of pathologies marked by the extracellular deposition of amyloid fibrils that considerably disrupt tissue architecture and thereby compromise normal organ function [33]. Even though multiple organ system involvement is typical, a single organ may be predominantly affected in variant forms of the disease [33]. Environmental toxins-particularly Cadmium, Lead, Manganese, and mercury-demonstrate a notable propensity to trigger amyloid aggregation [12]. This additional factor advances the current understanding of the mechanisms governing amyloid formation [73].

A β peptide aggregation serves as a paradigmatic example, as these peptides readily undergo aggregation, proceeding through soluble forms to filaments and ultimately to mature amyloid fibrils of undefined structure [74]. Synthetic membrane models of A β -related neurotoxicity have provided considerable insight into molecular interactions, emphasizing the role of membrane curvature and A β concentration-dependent effects in promoting aggregation [28]. Newly developed rapid A β more soluble oligomers drive fibrillogenesis at neuronal cell membranes; fibrils grow following the open ends of these seeded aggregates at the lipid bilayer [32]. Environmental toxin exposure thus reinforces the pathogenic cascade previously described in Alzheimer's disease [74].

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